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(54) Title: SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE

## (57) Abstract

This invention encompasses a modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising a pharmaceutical grade viscoelastic fraction selected from a group consisting of an acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms and mixtures of said acyl-substituted hyaluronic acid with hyaluronic acid, and hydroxypropylmethylcellulose. In particular these solutions have a surface tension of between 40 and 65 dynes/cm<sup>2</sup>; particularly a viscoelastic fraction has an average molecular weight of at least 50,000. In some embodiments a physiological buffer fraction is present. This invention further encompasses a method of using the claimed composition.

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1        SURFACE ACTIVE VISCOELASTIC SOLUTIONS FOR OCULAR USE

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Field of the Invention.

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This application is a continuation-in-part of copending U.S. Pat. App. 08/061,773 filed May 13, 1993, which is a continuation of U.S. Pat. App. 07/440,078 filed November 22, 1989, now abandoned.

The present invention relates to ophthalmic solutions for use during ocular and intraocular surgery, and more particularly to the use of surface active viscoelastic solutions during the extraction of a cataractous human lens and the implantation of a prosthetic ocular and intraocular lens. During surgery, the use of ophthalmic infusions with controlled physical properties, especially surface activity and viscoelastic properties, is advantageous for (1) replacing the fluid aqueous humor or ocular and intraocular air, (2) protecting the internal structures of the eye from accidental instrument or ocular and intraocular prosthetic device contact, (3) preventing irrigation damage by solutions used in routine cataract surgery, and (4) retarding aspiration from the eye of the viscoelastic solution during the surgical procedure. In addition, the invention relates to a method of adhering a contact lens to the surface of the eye, such as in association with procedures permitting a medical professional to view ocular and intraocular structures through the contact lens and through the viscoelastic solution. In

another application, the viscoelastic solution of this invention is used by injecting the solution into or under tissues within the eye, such as to dissect tissue off of the retina.

## Background of the Invention

In the past, biocompatible polymers used in ocular and intraocular surgery have been the naturally occurring mucopolysaccharides hyaluronic acid and chondroitin sulfate; mixtures of hyaluronic acid and chondroitin sulfate; and, cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC). Table 1 presents data reported in Viscoelastic Materials, Ed. E.S. Rosen, Proceedings of the Second International Symposium of the Northern Eye Institute, Manchester [U.K.], 17-19 July, 1986 (Pergamon Press, New York) as to the molecular weight of commercially available ocular products. Depending on the source from which these mucopolysaccharides are drawn, the molecular weights are estimated in the 50,000 range with the hyaluronic acid extending upwards to the  $8 \times 10^6$  range. Hyaluronic acid was first isolated and characterized by Meyer, Palmer and reported in the J. Biol. Chem., Vol. 107, p. 629 (1934) and Vol. 114, p.689 (1936) and by Balazs in the Fed. Proc. Vol. 17, p. 1086 (1958); and chondroitin sulfate by Bray et al. in Biochem. J. Vol. 38, p. 144 (1944); and Patat, Elias, Z. Physiol. Chem. vol. 316, p. 1 (1959).

Literature in the art describes the basic isolation and characterization of the viscoelastic solutions. It is a surprising feature of this invention which describes the control

1 of viscoelastic properties as related to the surface activity,  
2 or the solution fracturing under applied stress. In particular,  
3 it is surprising to manipulate or enhance the physical  
4 properties of viscoelastic solutions of mucopolysaccharides,  
5 hyaluronic acid, and/or chondroitin sulfate. It is believed  
6 that disclosure here of a processes to provide hyaluronic acid  
7 and species thereof with controlled surface activity is unique.  
8 This is also especially true of the control of surface activity  
9 of mucopolysaccharide solutions by the addition of biologically  
10 compatible surfactants. A characteristic feature of  
11 biologically compatible surfactants is the absence of observed  
12 alteration in cellular physiology upon contact. Early work in  
13 the viscoelastic field was presented by the inventor of this  
14 disclosure and his associates. Benedetto, D.A. et. al.,  
15 Viscoelastic Materials: Basic Science and Clinical Application,  
16 (Symposium Proceedings), University of Manchester, England, July  
17 17-19, 1986.

18  
19 As to commercial production, a review of the ophthalmic  
20 pharmacopoeia reveals there are several viscoelastic solutions  
21 produced for ocular and intraocular use during ophthalmic  
22 surgery. The most common application for these solutions is in  
23 the intraocular lens implant procedure for human cataract  
24 surgery. This procedure involves extraction of the cataractous  
25 human lens through a small surgical opening in the eye and the  
26 replacement of the lens by a prosthetic intraocular lens placed  
27 in situ. Biocompatible polymers presently or previously in use  
28 are hyaluronic acid (Healon™, Amvisc™); chondroitin sulfate, and

1 a combined solution of hyaluronic acid and chondroitin sulfate  
2 (Viscoat™); and a hydroxypropylmethylcellulose solution  
3 (Occucoat™). Research conducted recently demonstrates that  
4 Healon™ and Amvisc™ are not surface active, but Viscoat™ and  
5 Occucoat™ are.

6 Chondroitin sulfate does not exist as a free polysaccharide  
7 in its native state, but as a proteoglycan. It is obtained from  
8 sources associated with protein contaminants. The avoidance of  
9 chondroitin sulfate avoids a potential source of pyrogenic  
10 reaction, and the substantial cost associated with protein  
11 removal.

#### 12 Summary of the Invention

13 The invention presented herein discloses modified  
14 mucopolysaccharide or viscoelastic solutions for use as  
15 biologically active therapeutic infusions. In one form of the  
16 invention, the mucopolysaccharide solution is formed from a  
17 viscoelastic fraction and a buffer fraction. It has been found  
18 that when a new synthetic molecule acyl-substituted hyaluronic  
19 acid is employed as the viscoelastic fraction, control of  
20 surface activity is achieved. An indicia of this is the  
21 decrease of the surface tension of the solution which is now  
22 within predetermined limits discussed below. Surface tension  
23 modification is also accomplished with viscoelastic fractions in  
24 which the acyl-substituted hyaluronic acid is mixed with one or  
25 more of hyaluronic acid; and hydroxypropylmethylcellulose. In  
26 certain applications, the viscoelastic solution of this  
27 invention is used in a method of adhering a contact lens to the  
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1 surface of the eye, such as in association with procedures  
2 permitting a medical professional to view ocular and intraocular  
3 structures through the contact lens and through the viscoelastic  
4 solution. This is particularly useful in facilitating surgical  
5 procedures. In another application, the viscoelastic solution of  
6 this invention is used by injection the solution into or under  
7 structures or tissues within the eye, such as to dissect tissue  
8 off of the retina.

9  
10 In the broadest terms, surface active viscoelastic  
11 solutions with controlled solution properties, are characterized  
12 by surface tension, equilibrium contact angle, dynamic  
13 viscosity, and cohesiveness (the measure of solution fracture  
14 under stress). In a particular embodiment, this invention is  
15 delimited by the three dimensional representation of Fig. 7.

16 In one example, bioengineered hyaluronic acid from a  
17 bacterial source with an average molecular weight of 50,000 is  
18 modified by acyl substitution with three to twenty carbon atom  
19 acyl groups so that the resultant surface tension of such a  
20 solution is between 40 and 65 dynes/cm<sup>2</sup>. In the practice of  
21 this invention, a viscoelastic solution having a surface tension  
22 of less than about 56 dynes/cm<sup>2</sup>, and more particularly, less  
23 than about 50 dynes/cm<sup>2</sup> is of particular advantage.

24  
25 This invention comprises a modified mucopolysaccharide  
26 solution for use as a biologically active therapeutic infusion  
27 comprising:  
28

1 a pharmaceutical grade viscoelastic fraction selected from  
2 the group consisting of acyl-substituted hyaluronic acid having  
3 acyl groups thereof with three to twenty carbon atoms,  
4 hyaluronic acid, hydroxypropylmethylcellulose and mixtures  
5 thereof, and absent chondroitin sulfate said fraction having a  
6 surface tension of between 40 and 65 dynes/cm<sup>2</sup>; and,

7 optionally with a physiological buffer fraction, such that  
8 the viscoelastic comprises about a 0.1% percent of the solution  
9 to about 5% of the solution, by weight, and preferably from  
10 about 0.5 % to about 3%;

11 said modified mucopolysaccharide solution having a  
12 viscosity of between 10,000 and 100,000 centipoise when measured  
13 at a shear rate of 3 sec<sup>-1</sup> at 25°C; and,

14 optionally wherein the modified mucopolysaccharide  
15 solution has a surface tension of less than about 56 dynes/cm<sup>2</sup>,  
16 and further a surface tension of less than about 50 dynes/cm<sup>2</sup>;  
17 and further,

18 optionally wherein the solution has an osmolality of from  
19 about 250 to about 400 milliosmoles, or is generally isotonic  
20 with ophthalmic tissue.

21 In some embodiments the modified mucopolysaccharide  
22 solution viscoelastic fraction has an average molecular weight  
23 of at least 50,000. Reference is further made to the  
24 viscoelastic fraction being an acyl-substitute hyaluronic acid  
25 having acyl groups thereof with three to twenty carbon atoms.

26 In particular applications the modified mucopolysaccharide  
27 solution of this invention includes a surfactant fraction of a  
28 biocompatible component selected from a group consisting of



1 phospholipids, monoglycerides, free fatty acids, free fatty acid  
2 soaps, cholesterol, fluorocarbons, silicones, and nonionic  
3 surfactants, with the surfactant present in an amount sufficient  
4 to produce the required surface tension. In particular, a  
5 biological surfactant fraction of a free fatty acid is present  
6 in an amount of less than 1 mg/ml. Further embodiments include  
7 a surfactant fraction of a biocompatible component selected from  
8 a group consisting of phospholipids, monoglycerides, free fatty  
9 acids, free fatty acid soaps, cholesterol, fluorocarbons,  
10 silicones, and nonionic surfactants, said surfactant present in  
11 an amount less than 10 micrograms/ml. In a preferred embodiment  
12 the surfactant fraction of biocompatible component is a free  
13 fatty acid.

14 In a further embodiment the modified mucopolysaccharide  
15 solution has a viscoelastic fraction of a mixture of  
16 acyl-substituted hyaluronic acid and hyaluronic acid, and  
17 particularly with a surfactant fraction of a biocompatible  
18 component selected from a group consisting of phospholipids,  
19 monoglycerides, free fatty acids, free fatty acid soaps,  
20 cholesterol, fluorocarbons, silicones, and nonionic surfactants,  
21 with surfactant present in an amount sufficient to produce the  
22 required surface tension, usefully in an amount less than  
23 10 micrograms/ml. Preferred surfactants are free fatty acids  
24 such as oleic acid.

25 Particular modified mucopolysaccharide solutions of the  
26 invention are characterized by aspiration through a 0.3 mm  
27 cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and  
28 particularly in a range of 50 to 200 mm Hg, wherein the solution

1 is easily fractured. Similarly, those solutions with an  
2 aspiration profile of from about horizontal up to about 1.5 and  
3 more particularly from about horizontal to about 1.0 are  
4 preferred.

5 In another embodiment this present invention comprises a  
6 modified mucopolysaccharide solution for use during ophthalmic  
7 surgery for protection of the internal ocular structures  
8 including corneal endothelium from accidental touch by surgical  
9 instruments, yet permitting of observation of said structures  
10 comprising:

11 an optically clear polymeric fraction of high purity  
12 mucopolysaccharides selected from the group consisting of  
13 acyl-substituted hyaluronic acid having acyl groups thereof with  
14 three to twenty carbon atoms, hyaluronic acid,  
15 hydroxypropylmethylcellulose and mixtures thereof and absent  
16 chondroitin sulfate, said fraction having a surface tension of  
17 between 40 and 65 dynes/cm<sup>2</sup>; and,

18 optionally a physiological buffer fraction, such that the  
19 viscoelastic comprises about a 0.1% percent of the solution to  
20 about 5% of the solution, by weight, and preferably from about  
21 0.5 % to about 3%;

22 said modified mucopolysaccharide solution having a  
23 viscosity of between 10,000 and 100,000 centipoise when measured  
24 at a shear rate of 3 sec<sup>-1</sup> at 25 C; and,

25 wherein said mucopolysaccharide fraction has an average  
26 molecular weight of at least 50,000; and,

1 a biological surfactant fraction of a free fatty acid  
2 present in an amount less than 10 micrograms/ml; and,  
3 optionally wherein the modified mucopolysaccharide  
4 solution has a surface tension of less than about 56 dynes/cm<sup>2</sup>,  
5 and further a surface tension of less than about 50 dynes/cm<sup>2</sup>.

6 In some embodiment of this modified mucopolysaccharide  
7 solution a particular polymeric fraction is hyaluronic acid.

8 Particular modified mucopolysaccharide solutions of the  
9 invention are characterized by aspiration through a 0.3 mm  
10 cannula at a vacuum pressure in a range of 5 to 400 mm Hg, and  
11 particularly in a range of 50 to 200 mm Hg, wherein the solution  
12 is easily fractured, which optionally include those solutions  
13 with an aspiration profile of from about horizontal up to about  
14 1.5 and more particularly from about horizontal to about 1.0.

15 Another embodiment of the present invention includes a  
16 pharmaceutically acceptable modified mucopolysaccharide solution  
17 (particularly a surface active mucopolysaccharide) absent  
18 chondroitin sulfate having a surface tension of between 40 and  
19 65 dynes/cm<sup>2</sup>; and,

20 a viscosity of between 10,000 and 100,000 centipoise  
21 (particularly an average molecular weight of at least 50,000)  
22 when measured at a shear rate of 3 sec<sup>-1</sup> at 25 C.

23 optionally wherein the modified mucopolysaccharide  
24 solution has a surface tension of less than about 56 dynes/cm<sup>2</sup>,  
25 and further a surface tension of less than about 50 dynes/cm<sup>2</sup>.

26 In this embodiment of a modified mucopolysaccharide  
27 solution a particular polymeric fraction is hyaluronic acid.  
28

1        In certain applications the mucopolysaccharide solution  
2 further comprises a biological surfactant selected from a group  
3 consisting of phospholipids, monoglycerides, free fatty acids,  
4 free fatty acid soaps, cholesterol, fluorocarbons, silicones,  
5 and nonionic surfactants.

6        Yet a further embodiment of the invention includes a method  
7 of protecting internal ocular structures during ocular surgery  
8 and retarding aspiration of material from the ocular surgery  
9 site by the steps of:

10        intraocularly introducing biologically active therapeutic  
11 infusion amount of a modified mucopolysaccharide solution  
12 comprising:

13        a pharmaceutical grade viscoelastic fraction selected from  
14 the group consisting of acyl-substituted hyaluronic acid having  
15 acyl groups thereof with three to twenty carbon atoms,  
16 hyaluronic acid, hydroxypropylmethylcellulose and mixtures  
17 thereof and absent chondroitin sulfate, said fraction with a  
18 surface tension of between 40 and 65 dynes/cm<sup>2</sup> (particularly  
19 less than about 56 and more particularly less than about 50  
20 dynes/cm<sup>2</sup>); and,

21        optionally a physiological buffer fraction, such that the  
22 viscoelastic comprises about a 0.1% percent of the solution to  
23 about 5% of the solution, by weight, and preferably from about  
24 0.5 % to about 3%;

25        said modified mucopolysaccharide solution having a  
26 viscosity of between 10,000 and 100,000 centipoise when measured  
27 at a shear rate of 3 sec<sup>-1</sup> at 25 C. In such embodiment a  
28

1 preferred method entails intraocularly introducing biologically  
2 active therapeutic infusion amount of a modified  
3 mucopolysaccharide solution by a syringe of about  $1.13 \text{ cm}^2$  in  
4 cross section or less, and optionally about  $0.57 \text{ cm}^2$  or less,  
5 and further optionally about  $0.16 \text{ cm}^2$ . In certain embodiments a  
6 "sloped" syringe absent sharp reductions in cross sectional area  
7 is useful.

8 Further in this method the invention includes particular  
9 modified mucopolysaccharide solutions characterized by  
10 aspiration through a 0.3 mm cannula at a vacuum pressure in a  
11 range of 5 to 400 mm Hg, and particularly in a range of 50 to  
12 200 mm Hg, wherein the solution is easily fractured. Similarly,  
13 those solutions with an aspiration profile of from about  
14 horizontal up to about 1.5 and more particularly from about  
15 horizontal to about 1.0 are preferred.

16 An additional embodiment of the invention includes a method  
17 of protecting internal ocular structures during ocular surgery  
18 by providing a viscoelastic solution that coats ocular  
19 structures at a surgical site such that aspiration of the  
20 viscoelastic solution is retarded, said method being:

21 intraocularly introducing biologically active therapeutic  
22 infusion amount of a modified mucopolysaccharide solution absent  
23 chondroitin sulfate and having a surface tension of between 40  
24 and  $65 \text{ dynes/cm}^2$  (particularly less than about 56 and more  
25 particularly less than about  $50 \text{ dynes/cm}^2$ ); and,  
26

27  
28

1 a viscosity of between 10,000 and 100,000 centipoise when  
2 measured at a shear rate of  $3 \text{ sec}^{-1}$  at 25 C. In such embodiment  
3 a preferred method entails intraocularly introducing  
4 biologically active therapeutic infusion amount of a modified  
5 mucopolysaccharide solution by a syringe of about  $1.13 \text{ cm}^2$  in  
6 cross section or less, and optionally about  $0.57 \text{ cm}^2$  or less,  
7 and further optionally about  $0.16 \text{ cm}^2$ .

8 Further in this method the invention includes particular  
9 modified mucopolysaccharide solutions characterized by  
10 aspiration through a 0.3 mm cannula at a vacuum pressure in a  
11 range of 5 to 400 mm Hg, and particularly in a range of 50 to  
12 200 mm Hg, wherein the solution is easily fractured. Similarly,  
13 those solutions with an aspiration profile of from about  
14 horizontal up to about 1.5 and more particularly from about  
15 horizontal to about 1.0 are preferred.

16 A next method of the present invention includes a method of  
17 protection of internal ocular structures including corneal  
18 endothelium from accidental touch by surgical instruments, yet  
19 permitting of observation of said structures comprising:

20 intraocularly introducing a modified mucopolysaccharide  
21 solution during ophthalmic surgery wherein said solution  
22 comprises

23 an optically clear polymeric fraction of high purity  
24 mucopolysaccharides selected from the group consisting of  
25 acyl-substituted hyaluronic acid having acyl groups thereof with  
26 three to twenty carbon atoms, hyaluronic acid,  
27 hydroxypropylmethylcellulose and mixtures thereof and absent  
28

1 chondroitin sulfate, said fraction having a surface tension of  
2 between 40 and 65 dynes/cm<sup>2</sup> (particularly less than about 56 and  
3 more particularly less than about 50 dynes/cm<sup>2</sup>); and,

4 optionally a physiological buffer fraction, such that the  
5 viscoelastic comprises about a 0.1% percent of the solution to  
6 about 5% of the solution, by weight, and preferably from about  
7 0.5 % to about 3%;

8 said modified mucopolysaccharide solution having a  
9 viscosity of between 10,000 and 100,000 centipoise when measured  
10 at a shear rate of 3 sec<sup>-1</sup> at 25 C; and,

11 wherein said mucopolysaccharide fraction has an average  
12 molecular weight of at least 50,000; and,

13 a biological surfactant fraction of a free fatty acid  
14 present in an amount less than 10 micrograms/ml.

15 In such embodiment a specific method entails intraocularly  
16 introducing biologically active therapeutic infusion amount of a  
17 modified mucopolysaccharide solution by a syringe of about 1.13  
18 cm<sup>2</sup> in cross section or less, and optionally about 0.57 cm<sup>2</sup> or  
19 less, and further optionally about 0.16 cm<sup>2</sup>.

20 Further in this method the invention includes particular  
21 modified mucopolysaccharide solutions characterized by  
22 aspiration through a 0.3 mm cannula at a vacuum pressure in a  
23 range of 5 to 400 mm Hg, and particularly in a range of 50 to  
24 200 mm Hg, wherein the solution is easily fractured. Similarly,  
25 those solutions with an aspiration profile of from about  
26 horizontal up to about 1.5 and more particularly from about  
27 horizontal to about 1.0 are preferred.

28

1       A next embodiment of the invention comprises a modified  
2 mucopolysaccharide solution for use as a biologically active  
3 therapeutic infusion comprising:

4       a pharmaceutical grade viscoelastic fraction selected from  
5 the group consisting of acyl-substituted hyaluronic acid having  
6 acyl groups thereof with three to twenty carbon atoms,  
7 hyaluronic acid, hydroxypropylmethylcellulose and mixtures  
8 thereof, and absent chondroitin sulfate said fraction having a  
9 surface tension of between 40 and 65 dynes/cm<sup>2</sup> (particularly  
10 less than about 56 and more particularly less than about 50  
11 dynes/cm<sup>2</sup>); and,

12       said modified mucopolysaccharide solution having a  
13 viscosity of between 10,000 and 100,000 centipoise when measured  
14 at a shear rate of 3 sec<sup>-1</sup> at 25°C.

15       This invention encompasses a modified mucopolysaccharide  
16 solution for use as a biologically active therapeutic infusion  
17 comprising:

18       a pharmaceutical grade viscoelastic fraction selected from  
19 a group consisting of an acyl-substituted hyaluronic acid having  
20 acyl groups thereof with three to twenty carbon atoms and  
21 mixtures of said acyl-substituted hyaluronic acid with  
22 hyaluronic acid, chondroitin sulfate A, chondroitin sulfate B,  
23 chondroitin sulfate C, and hydroxypropylmethylcellulose, said  
24 fraction with a surface tension of between 40 and 65 dynes/cm<sup>2</sup>;  
25 particularly a viscoelastic fraction has an average molecular  
26 weight of at least 50,000; and,  
27  
28



1 optionally a physiological buffer fraction, such that the  
2 viscoelastic comprises about a 0.1% percent of the solution to  
3 about 5% of the solution, by weight, and preferably from about  
4 0.5 % to about 3%;

5 whereby, upon infusion of modified mucopolysaccharide  
6 solution at the site, the surface activity of the solution  
7 enhances coating of the site.

8 A specific modified mucopolysaccharide solution is one with  
9 an acyl-substituted hyaluronic acid, and a preferred viscosity  
10 is between 10,000 and 100,000 centipoise when measured at a  
11 shear rate of  $3 \text{ sec}^{-1}$  at  $25^{\circ}\text{C}$ , and optionally further including  
12 a surfactant fraction of a biocompatible component selected from  
13 a group consisting of phospholipids, monoglycerides, free fatty  
14 acids, free fatty acid soaps, cholesterol, fluorocarbons,  
15 silicones, and nonionic surfactants, said surfactant present in  
16 a trace amount sufficient to produce said surface tension. In  
17 one embodiment the surfactant is present in an amount less than  
18 10 micrograms/ml. A preferred surfactant is oleic acid. A  
19 preferred modified mucopolysaccharide solution comprises a  
20 mixture of an acyl-substituted hyaluronic acid and hyaluronic  
21 acid.

22 In a particular application this invention includes a  
23 modified mucopolysaccharide solution for use a biologically  
24 compatible therapeutic infusion comprising:

25 a pharmaceutical grade viscoelastic fraction selected from  
26 a group consisting of hyaluronic acid, chondroitin sulfate A,  
27 chondroitin sulfate B, and chondroitin sulfate C, said fraction  
28 having an average molecular weight of at least 50,000.

1 a surfactant fraction of a biocompatible component selected  
2 from a group consisting of phospholipids, monoglycerides, free  
3 fatty acids, free fatty acid soaps, cholesterol, fluorocarbons,  
4 silicones, and nonionic surfactants, said surfactant present in  
5 a trace amount sufficient to produce a surface tension of  
6 between 40 and 65 dynes/cm<sup>2</sup>; and,

7 optionally a physiological buffer fraction, such that the  
8 viscoelastic comprises about a 0.1% percent of the solution to  
9 about 5% of the solution, by weight, and preferably from about  
10 0.5 % to about 3%;

11 whereby, upon infusion of modified mucopolysaccharide  
12 solution at the site, the surface activity of the solution  
13 enhances coating of the site and results in retardation of  
14 aspiration at the site. A preferred modified mucopolysaccharide  
15 solution has a viscoelastic fraction of hyaluronic acid, and,  
16 optionally, a viscosity of between 10,000 and 100,000 centipoise  
17 when measured at a shear rate of 3 sec<sup>-1</sup>, and further  
18 optionally, a surfactant, particularly oleic acid, and  
19 particularly with surfactant present in an amount less than 10  
20 micrograms/ml.

21 In one embodiment this invention includes a modified  
22 mucopolysaccharide solution for use during ophthalmic surgery  
23 for protection of the internal ocular structures comprising:

24 an optically clear polymeric fraction of high-purity  
25 mucopolysaccharides and mixtures thereof, said polymeric  
26 fraction selected from the group consisting of hyaluronic acid,  
27 chondroitin sulfate A, chondroitin sulfate B, chondroitin

28

1 sulfate C, and mixtures of hyaluronic acid, chondroitin sulfate  
2 A, chondroitin sulfate B and chondroitin sulfate C with an  
3 average molecular weight of at least 50,000;

4 a biological surfactant fraction of a free fatty acid  
5 present in an amount of less than 1 mg/ml; and,

6 optionally a physiological buffer fraction, such that the  
7 viscoelastic comprises about a 0.1% percent of the solution to  
8 about 5% of the solution, by weight, and preferably from about  
9 0.5 % to about 3%;

10 whereby, upon the modified mucopolysaccharide solution  
11 being placed in the eye space during surgery, the surgeon can  
12 observe the ocular and intraocular structure through the  
13 optically clear solution, and the corneal endothelium is  
14 protected from accidental touch by surgical instruments, ocular  
15 and intraocular prosthetic devices, and in ocular and  
16 intraocular irrigating solutions, particularly wherein the  
17 polymeric fraction is hyaluronic acid, and particularly wherein  
18 the solution has a viscosity of between 10,000 and 100,000  
19 centipoise when measured at a shear rate of  $3 \text{ sec}^{-1}$  at  $25^{\circ}\text{C}$ .

20 An additional embodiment of this invention is a method of  
21 adhering a contact lens to the surface of the eye in  
22 operational-optical connection with said eye, by the step of  
23 interposing between said lens and said eye surface an adhering  
24 amount of substantially transparent modified mucopolysaccharide  
25 solution of this invention. In the practice of this method, an  
26 apparatus comprising a contact lens and a layer of transparent  
27 modified mucopolysaccharide solution is employed. Preferably  
28 the optical properties of such lens/solution unit will be

1 configured to facilitate observation of internal ophthalmic  
2 structures when the observer is positioned to peer directly  
3 through the lens. Alternatively, the "observer" may be a  
4 television, film or other camera directed into the lens.  
5 Further, the camera lens may substitute for the contact lens,  
6 and thus with a layer of the mucopolysaccharide solution of this  
7 invention, be in direct contact with the eye.

8       A yet further embodiment of this invention is a method of  
9 hydraulically positioning intra-optic structures or tissues by  
10 the step of applying against such tissues under elevated  
11 hydrostatic pressure the modified mucopolysaccharide solution of  
12 this invention. Typically this would be applied to dissect or  
13 elevate hyperplastic tissue that grows over the retina in  
14 certain pathologies. The degree of elevation of hydrostatic  
15 pressure would be that sufficient to move the intended tissue.

16       An additional aspect of this invention is based upon  
17 ophthalmic osmolality. Osmolality of from about 250  
18 milliosmoles to about 400 milliosmoles is essentially isotonic  
19 to optic structures. Lower osmolality will cause optic  
20 structures to swell and higher osmolality will cause shrinkage.

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2                   **Brief Description of the Drawings**

3           Fig. 1 is a plot of  $Kc/R_g$  against concentration, C. The  
4 material tested is high molecular weight HA. The molecular  
5 weight was obtained from the inverse of the abscissa  
6 extrapolated to zero concentration.

7           Fig. 2 is a plot of maximum load versus time for high  
8 molecular weight HA. The maximum load was determined as the  
9 largest load needed to force a sample of viscoelastic from a  
10 syringe through a 23 gauge needle.

11           Fig. 3. is a graphic comparison of the surface tension of  
12 one embodiment of of a solution of the present invention as  
13 compared to the surface tension of a commercially available HPMC  
14 ocular solution, and a commercially available HA ocular  
15 solution.  
16

17           Fig. 4 is a graphic comparison of the viscosity of one  
18 embodiment of a solution of the present invention as compared  
19 with other, commercially available, ocular solutions, and  
20 measured at a shear rate of  $0.35 \text{ sec}^{-1}$ . Standard deviation is  
21 shown in gray, and the average values in black. All columns  
22 except E and F are statistically different than B, Healon™

23           Fig. 5 is a plot comparison of the aspiration  
24 characteristics of the *in situ* retention of solutions embodying  
25 the present invention as compared other viscoelastic ocular  
26 solutions.  
27

28           Fig. 5(a) repeats Fig. 5 with a preferred range shaded.

1           Fig. 6 is a plot of viscosity against surface tension  
2 enclosing a preferred range for solutions of the present  
3 invention.  
4

5           Fig. 7 is a three dimensional plot of viscosity against  
6 surface tension against "aspiration profile" (the slope of the %  
7 of aspiration between 50 mmHg and 90 mmHg under test conditions  
8 as plotted in Fig. 5, and excluding sigmoidal curves) enclosing  
9 in cubic representation a of viscoelastic solutions of the  
10 present invention.

11           Fig. 8 is a graphic representation of stress (MPa) recorded  
12 by injecting various solutions of varying viscosity from a  
13 syringe and through a 23 gauge needle.  
14

15           Fig. 9(a), (b), and (c) represent various embodiments of  
16 "sloped" syringe absent sharp reductions in cross sectional  
17 area.

18           Fig. 10(a) and (b) are diagrammatic representations of  
19 various embodiments of an apparatus for viewing the interior of  
20 the eye (depicted in contact with an eye).  
21

## 22                           Detailed Description of the Invention

23           In general terms, viscoelastic solutions are placed in the  
24 anterior chamber of the eye during ocular and intraocular lens  
25 implant surgery, replacing the fluid aqueous humor of the eye.  
26 Clearly, hosts suitable for application of the present materials  
27 and methods are ocular and intraocular site of animal requiring  
28

1 such material. In particular, host sites are mammalian eyes,  
2 particularly those of humans, and most particularly the anterior  
3 chamber thereof. By nature of their viscosity (10,000 to 1  
4 million times greater than that of aqueous humor), viscoelastic  
5 solutions allow the eye to maintain its normal shape and ocular  
6 and intraocular structural relationships during cataract  
7 extraction and lens implantation. When the fluid aqueous humor  
8 leaks from the eye, as when the eye is opened by incision at the  
9 time of surgery, the anterior structures of the eye collapse.

10 There is no space within the anterior segment of the eye within  
11 which the surgeon can place instruments for cataract extraction  
12 without damaging ocular and intraocular structures by touch from  
13 his instruments. Air may be used to maintain this space, but it  
14 is more likely to leak from the eye compared to a viscous  
15 solution. In addition, air on top of other ocular fluids, does  
16 not allow the surgeon to visualize ocular and intraocular  
17 structures, as effectively as through clear viscoelastic  
18 solution. Viscoelastic solutions are fluids which resist flow  
19 by nature of their high viscosity. These fluids are elastic  
20 because they have a "memory." They return to approximately  
21 their original shape after stretch. These solutions are  
22 optically clear and are basically aqueous solutions of higher  
23 molecular weight polymers in the molecular weight range of  
24 50,000 to 8 million.

25 As used herein, in reference to HPMC, the term "low" in  
26 reference to "low molecular weight" HPMC, "HPMC(L)," shall mean  
27 below about 250,000 MW and particularly below about 150,000 MW,  
28 while "high" molecular weight HPMC, "HPMC(H)," shall mean above

1 about 250,000 MW and particularly above about 300,000 MW. In  
2 reference to HA, the term "low" in reference to "low molecular  
3 weight" HA, "HA(L)," shall mean below about 1,500,000 MW, and  
4 particularly below about 700,000 MW, while "high" molecular  
5 weight HA, "HA(H)," shall mean above about 1,500,000 MW, and in  
6 particular above about 3,000,000 MW, and more particularly above  
7 about 5,000,000 MW.

8 In addition to being viscous and elastic, a mild degree of  
9 surface activity is a desirable property of viscoelastic  
10 solutions. Surface activity is a measure of the ability of a  
11 solution to coat or spread on a surface. Solutions which coat  
12 the internal structures of the eye are better able to protect  
13 the eye from accidental touch by surgical instruments or an  
14 intraocular lens. In addition, these solutions protect the eye  
15 from irrigation damage by irrigating solutions used in routine  
16 cataract surgery. Viscoelastic solutions which are not surface  
17 active and do not fracture at aspiration pressures used during  
18 cataract surgery are too easily aspirated from the eye during  
19 cataract surgery. The surgeon is then faced with lack of  
20 protective ophthalmic solution, which necessitates replacement  
21 of viscoelastic at additional cost.  
22

23 Particular note is made of the distinction between  
24 viscosity and pseudoplasticity (which includes thixotropy).  
25 Viscosity is the propensity of a solution to resist flow.  
26 Pseudoplasticity is the general case of a change in viscosity  
27  
28



1 with applied force, which may or may not be reversible.  
2 Thixotropy describes reversible shear thinning, limited largely  
3 to the period while subject to shear.

4  
5 Surface tension is a measure of the tendency of molecules  
6 within a solution to attract or repel each other. With high  
7 mutual attraction, the solution has a high surface tension and  
8 the solution is cohesive. Without being bound by any particular  
9 theory, it is believed that at a solution interface (air/liquid,  
10 liquid/liquid, liquid/solid) of a solution of high surface  
11 tension, the tendency would be for solution molecules to be  
12 drawn back into the solution. In a solution of low surface  
13 tension (i.e., a surfactant type solution) solution molecules  
14 accumulate at an interface because the molecules are not  
15 completely soluble within the bulk solution. It is presumed  
16 that the hydrophobic/hydrophilic structure of surfactant  
17 molecules cause them to accumulate at a solution interface,  
18 representing the lowest energy state.

19 Particular attention is drawn to the unique confluence of  
20 physical characteristics present in the viscoelastic solution of  
21 the present invention. Considering viscosity, Fig. 4 discloses  
22 that a variety of viscosities (Fig. 4, Examples E-H) may be  
23 obtained within the practice of this invention, while still  
24 presenting the required surface tension and aspiration profile.  
25 Viscosity is presented in m Pa·s or millipascal·seconds. One  
26 Pa·s equals 1000 centipoise, and one mPa·s equals 1 centipoise.  
27 Fig 4. data was obtained at a shear rate of  $0.35 \text{ sec}^{-1}$ . The  
28 solutions represented are as follows: A is 2% HPMC(L) and a

1 molecular weight of about 200,000 with a viscosity of 98 cps; B  
2 is 2% HPMC with a viscosity of 3680 cps; C is 1% HA(L) (L  
3 denotes an average MW of about  $0.8 \times 10^6$ ) solution with a  
4 viscosity of 424 cps; D is 1% HA(H) (H denotes an average MW of  
5 about  $2.1 \times 10^6$ ) solution with a viscosity of 21,845 cps; E is a  
6 mixture of 2% HPMC(L) and 1% HA(L) with a viscosity of 2,095  
7 cps; F is a mixture of 2% HPMC(L) and 1% HA(H) with a viscosity  
8 of 38,460 cps; G is a mixture of 2% HPMC(H) and 1% HA(L) with a  
9 viscosity of 25,344 cps; and H is a mixture of 2% HPMC(H) and 1%  
10 HA(H) with a viscosity of 56,691 cps. The substantial and  
11 synergistic increase in HPMC viscosity in combination with a  
12 viscoelastic, such as, HA is noted.

13  
14 Fig. 3 compares the surface tension of various ocular  
15 solutions. Solution A is Occucoat™, a commercially available  
16 HPMC solution, measured at 1:10 dilution as having a surface  
17 tension of  $43.0 \pm 1.41$  dynes/cm; Solution B is Healon™, a  
18 commercially available HA solution, measured at  $62.7 \pm 6.51$   
19 dynes/cm, Solution C, low molecular weight HPMC, and Solution D,  
20 high molecular weight HPMC were measured at about  $50 \pm .75$   
21 dynes/cm; Solution E, low molecular weight HA, and Solution F,  
22 high molecular weight HA were measured at about  $70 \pm 2.25$   
23 dynes/cm; Solutions G through J are mixtures of 1% HA and 2%  
24 HPMC all having a surface tension of about  $50 \pm 0.58$  dynes/cm .  
25 Specifically Solution G is HA(L) and HPMC(L). Solution H is  
26 HA(H) and HPMC(L). Solution I is HA(L) and HPMC(H). Solution J

1 is HA(H) and HPMC(H). Note that Fig. 3 solutions A, C, D, G-J  
2 exhibit surface tension statistically significantly different  
3 than B, Healon™.

4 Further note is made of the fracture and aspiration  
5 characteristics of the mucopolysaccharide solutions of this  
6 invention. In ocular surgery, a tiny cannula is used to  
7 inject/remove viscoelastic solutions. The claimed solutions  
8 easily fracture when vacuum is applied by a cannula. Thus to  
9 remove all of such solution, the cannula must be repeatedly  
10 moved to remain in contact with the solution. In contrast, a  
11 typical solution of high molecular weight as known in the prior  
12 art fall into two groupings. One, typified by Healon™, an HA  
13 solution will not fracture easily, nor will it elute in  
14 solutions typically present during ophthalmic surgery and  
15 generally aspirates only in a bolus. The other grouping  
16 comprises solutions "incohesive" solutions. "Incohesive"  
17 solutions elute so rapidly that, they are removed from the  
18 ocular surgical site by irrigation fluids. This rapid elution  
19 destroys the viscosity, coating and shock absorbing properties  
20 for which they were being used, leaving the field unprotected.

21 A useful measure of fracture and aspiration characteristics  
22 of various solutions is set forth in Fig. 5. In particular,  
23 Fig. 5 is a clear representation of the achievement of  
24 protective *in situ* retention of a solution embodying the present  
25 invention as compared to an HA ocular solution -- independent of  
26 viscosity. The aspiration behavior of HA is seen to be  
27 generally sigmoidal. At low vacuum, only small amounts of HA  
28

1 are aspirated, while at vacuums of about 40 mm Hg, almost 100%  
2 of the HA is removed. In contrast, a mixture of HA and HPMC, is  
3 removed in a manner generally linear to the amount of vacuum  
4 applied, permitting gradual removal, which may be continued to  
5 almost total removal, but not removal generally as a single  
6 bolus. Again, this linear removal profile may be obtained with  
7 solutions of a viscosity similar to that of HA alone, and  
8 substantially above the viscosity of HPMC alone. Particularly  
9 useful viscoelastic solutions are those whose aspiration  
10 characteristics are non-sigmoidal under the described  
11 experimental conditions, and most particularly those which are  
12 generally linear with a slope of between about horizontal and  
13 about 1.5, (and preferably between about horizontal and about 1)  
14 as presented in Fig. 5 as percentage aspiration against mmHG  
15 from about 50 mm HG to about 90 mm HG, using a 23 gauge needle.  
16 The procedure is more fully described in Aspiration Profile  
17 (below). A preferred range is shaded in Fig. 5(a) which  
18 reproduces Fig 5.

19 Figs. 6 and 7 define meets and bounds of particular  
20 embodiments of this invention. Fig. 6 is seen to delimit  
21 suitable viscoelastics by viscosity and surface tension.  
22 Particularly preferred are those solutions of less than 56  
23 dynes/cm and more particularly, those of less than 50 dynes/cm  
24 surface tension. Occucoat™ is plotted as point "I" and Healon™  
25 is plotted as point "II." Fig. 7 graphically distinguishes the  
26 chondroitin free viscoelastic solution of the present invention  
27 from particular commercial viscoelastic solutions. Three  
28

1 parameters, viscosity, surface tension, and aspiration profile  
2 are presented. It is the three dimensional area circumscribed  
3 by these parameters that are particularly useful. More  
4 particularly is the circumscribed area, below 56 dynes/cm in  
5 surface tension and more particularly still, the circumscribed  
6 area below 50 dynes/cm surface tension.

7  
8 Given the delimiting parameters of the claimed viscoelastic  
9 solutions, a general protocol to achieve such solutions is  
10 presented. Viscosity is increased or decreased in relation to  
11 highest molecular weight viscoelastic material or polymeric  
12 material present. If the viscosity of that highest molecular  
13 weight material is the viscosity desired, no adjustment is  
14 required. If lower viscosity is desired, increased dilution, or  
15 substitution of material of identical structure, but lower  
16 molecular weight, decreases viscosity. When increasing  
17 dilution, attention must be paid to the resulting solution  
18 osmolarity. Aspiration characteristics of the invention are  
19 modified by admixing viscoelastic polymers with low molecular  
20 weight polymers of the same or other species, including  
21 polysaccharides such as HPMC. Such additions increase ease of  
22 fracture on aspiration. Surface tension is reduced by addition  
23 of surfactant or by modification of a non-surface active  
24 molecule to be surface active. Particular note is made of the  
25 surface activity of HPMC. In the case of HA, surface activity  
26 adjustment entails addition of a lipophilic acyl side chain or  
27 chains. Osmolality is adjusted by modification of the  
28 solute/solvent ratio.

1 All of the foregoing parameters are most easily adjusted by  
2 empirical methods such as a checkerboard type assay, increasing  
3 the amount of each particular factor (serial dilution) until the  
4 desired characteristic is obtained. However, approximate  
5 methods of calculation are possible.

6 By this disclosure, non-surface active viscoelastic  
7 solutions are modified to make them surface active. This can be  
8 accomplished by the addition of any one of many biocompatible  
9 surfactants, or by substitution or admixture of hyaluronic acid  
10 polymer in a viscoelastic solution with hyaluronic acid polymer  
11 having a lipophilic side chain. A lipophilic acyl side chain  
12 substituted hyaluronic acid renders the previously completely  
13 water soluble molecule surface active. Biological surfactants  
14 belong to the following categories of chemical substances:  
15 phospholipids, monoglycerides, free fatty acids or fatty acid  
16 soaps, cholesterol, and pharmaceutical grade nonionic  
17 surfactants. Though it is understood that HPMC has some  
18 surfactant activity, as used herein, biological surfactants  
19 excludes HPMC. Preliminary results with oleic acid, a fatty  
20 acid component of phospholipids which composes most mammalian  
21 cell membranes, indicate that at a concentration of 1 microgram  
22 oleic acid per ml of solution can provide moderate surface  
23 activity to a solution which was not previously surface active.  
24 During routine cataract surgery, particular claimed viscoelastic  
25 solutions with surface activity will coat ocular, and  
26 intraocular structures, and a prosthetic lens during its  
27 placement into the eye.  
28

1           In the present invention, a modified mucopolysaccharide  
2 solution is disclosed. The modified mucopolysaccharide solution  
3 is used as a biologically active therapeutic infusion, most  
4 typically during ophthalmic surgery, such as one ocular and  
5 intraocular lens implant procedure. In a specific mode of  
6 practicing the present invention, the mucopolysaccharide  
7 solution includes a pharmaceutical grade viscoelastic fraction  
8 which is selected preferably from hyaluronic acid or an  
9 acyl-substituted hyaluronic acid or mixtures of acyl-substituted  
10 hyaluronic acid and hyaluronic acid with HPMC and optionally  
11 with a biocompatible surfactant; and,  
12 hydroxypropylmethylcellulose (HPMC), and absent chondroitin  
13 sulfate A, B, or C. The acyl-substituted hyaluronic acids have  
14 alky groups with three to twenty carbon atoms. Besides the  
15 viscoelastic fraction, the mucopolysaccharide solution usually  
16 includes a physiological buffer fraction, conveniently in a  
17 predetermined ratio to reach a suitable osmotic level. A  
18 solution of between about 250 and about 400 milliosmoles is  
19 generally isotonic to ocular tissues. Of course, solutions of  
20 higher osmolality will potentially cause a net solute outflow  
21 from ocular tissues while those of lower osmolality may permit  
22 net solute migration into such tissues. When the physical  
23 properties, especially surface activity, of the modified  
24 mucopolysaccharide solution are closely controlled, infusion and  
25 aspiration at the site of an ophthalmic operation are more  
26 manageable and, particularly, the coating at the site of  
27 solution contact is enhanced. In order for a solution, gel, or  
28

1 the like, including mucopolysaccharide solutions of the present  
2 invention, (collectively "coating agents") to coat a surface,  
3 the surface tension of the coating agent must be lower than the  
4 critical surface tension of the surface to be coated. Human  
5 corneal endothelium is frequently found to have a critical  
6 surface tension of from about 50 to about 56 dynes/cm<sup>2</sup>. Thus,  
7 in the practice of this invention, a coating agent having a  
8 surface tension of less than about 56 dynes/cm<sup>2</sup>, and more  
9 particularly, less than about 50 dynes/cm<sup>2</sup> is of particular  
10 advantage.

11 In addition to the above, another modified  
12 mucopolysaccharide solution is disclosed. The second modified  
13 mucopolysaccharide solution is used during ophthalmic surgery  
14 for protection of the internal ocular structures, most typically  
15 during extraction of a cataractous human lens and the  
16 replacement thereof by a prosthetic intraocular lens. In  
17 practicing the second embodiment of the invention, the  
18 mucopolysaccharide solution includes an optically clear  
19 polymeric fraction which is selected preferably from hyaluronic  
20 acid; and mixtures of hyaluronic acid, and absent chondroitin  
21 sulfate A, chondroitin sulfate B, and chondroitin sulfate C.

22 In the alternative, modified mucopolysaccharide solution, a  
23 second fraction is that of a biologically compatible surfactant.  
24 As will be described infra, many free fatty acid and similar  
25 surfactants are utilizable in trace quantities to lower the  
26 surface tension into the desired range. Besides the  
27 viscoelastic and surfactant fractions, mucopolysaccharide  
28



1 solution includes a physiological buffer fraction in a  
2 predetermined ratio between the weight of the viscoelastic  
3 fraction (surfactant fraction is not significant in the ratio)  
4 and the weight of the buffer fraction. While the physical  
5 properties of the modified mucopolysaccharide solution are  
6 closely controlled, upon the modified mucopolysaccharide  
7 solution being placed in the anterior chamber of the eye during  
8 surgery, the surgeon can observe the ocular and intraocular  
9 structure through the optically clear solution, and the corneal  
10 endothelium is coated and thereby protected from accidental  
11 touch by surgical instruments, ocular and intraocular prosthetic  
12 devices, and in ocular and intraocular irrigating solutions.

13       Practitioners in the art frequently attempt to use  
14 mucopolysaccharide solutions of particularly high viscosity.  
15 However, the use of such high viscosity mucopolysaccharide  
16 solutions has been limited by the difficulty encountered in  
17 injecting such solutions. Frequently such solutions have not  
18 been injectable at forces obtainable in hand held syringes. It  
19 has now been discovered that the stress and force required to  
20 inject mucopolysaccharide solutions, that is solutions  
21 containing macromolecules such as HA and HPMC, decreases as  
22 syringe size decreases. Thus syringe injecting a  
23 mucopolysaccharide solution of given viscosity, through a needle  
24 of given size, e.g. a 23 gauge needle, a 1cc syringe requires  
25 substantially less force than a 3 cc syringe and a 3 cc syringe  
26 less than a 5 cc syringe. (This generally presumes the standard  
27 syringe configurations of inside cross section of 0.16 cm<sup>2</sup> for a  
28

1 1cc syringe, 0.57 cm<sup>2</sup> for a 3cc and 1.13 cm<sup>2</sup> for a 5 cc  
2 syringe.) Fig. 8 provides an exemplary table of such forces.  
3 Solutions compared are A, HPMC(H); B, HA(H);, C, HA(L); D,  
4 HPMC(H) and HA(L); and, E, HPMC(H) and HA(H). Clearly, the 1cc  
5 syringe required less stress at maximum than the wider syringes.

6 Fig. 9(a) depicts a syringe (10) and plunger (12) with a  
7 generally flat lower surface (13) particularly useful in the  
8 practice of this invention. The angle  $\theta$  of the flow path for a  
9 viscoelastic through the syringe within the syringe into a  
10 cannula (14) is seen to be about 45° or less. Fig. 9(b) depicts  
11 an alternative plunger (16) for syringe (10). The lower surface  
12 (18) of plunger (16) is shaped to generally conform to angle  $\theta$   
13 at the bottom of syringe (10). A related embodiment is seen in  
14 Fig. 9(c), wherein a syringe (20) and plunger (22) with a  
15 generally bulbous lower surface (24). The flow path for a  
16 viscoelastic through lower end of the syringe within the syringe  
17 into a cannula (14) is seen to be about 45° or less, but sloped  
18 and not linear. Unlike the usual regimen associated with  
19 administration of medicaments through a syringe, the "dosage"  
20 delivered here is determined by observation of the material  
21 extruded from the end of the syringe. As such the amount  
22 initially in a syringe or remaining in a "dead space" within the  
23 syringe and not extrudable by application of pressure on the  
24 plunger is of little consequence. This presumes that there is  
25 sufficient extrudable capacity of viscoelastic mater to begin  
26 with.

27

28

1       An embodiment of this invention is drawn to a method of  
2       adhering a contact lens to the surface of the eye, and the  
3       apparatus of such method. This is done to permit a medical  
4       professional to clearly observe the interior of the eye. That  
5       is the contact lens is typically designed for a person other  
6       than the subject of the medical procedure to see into the eye.  
7       To accomplish this a lens of appropriate optics and conformance  
8       to corneal curvature is positioned in on the eye wherein the eye  
9       surface is coated with a generally continuous sheet or layer of  
10      the viscoelastic solution of this invention. In this  
11      application it is particularly important that the viscoelastic  
12      solution be generally transparent and bubble free. The  
13      arrangement of lens on top of such viscoelastic, on top of the  
14      eye permitting a view of the interior of the eye by a person  
15      other than the subject is termed "operational-optical  
16      connection."

17      Fig 10(a) (60) and (b) (70) are diagrammatic  
18      representations of various embodiments of an apparatus for  
19      viewing the interior of the eye (depicted in contact with an eye  
20      (50)). Fig. 10(a) represents a side view of contact lens (64)  
21      atop a layer of transparent mucopolysaccharide solution of the  
22      present invention (62), positioned and optically configured so  
23      that an external observer may view internal ophthalmic tissues,  
24      surgical instruments, color reactions, or other observable  
25      features or phenomena. Fig. 10(b), also having a layer of  
26      transparent mucopolysaccharide solution of the present invention  
27      (72), replaces the contact lens with the lens (74) of a camera  
28      (76). In an additional embodiment, the camera could include a

1 source of illumination or laser surgical light, or be replaced  
2 by or used in combination with a source of illumination or laser  
3 light, such as surgical laser light, or even diagnostic light  
4 application.

5 An embodiment of this invention concerns method of  
6 hydraulically positioning intra-optic structures or tissues.  
7 This is done by the step of applying against such tissues under  
8 elevated hydrostatic pressure the modified mucopolysaccharide  
9 solution of this invention. In one case, this comprises keeping  
10 the lens capsule elevated and away from surgical instruments  
11 during surgery such as cataract surgery. In another embodiment  
12 this method would include dissecting or elevating tissue such as  
13 hyperplastic tissue that has grown over the retina in certain  
14 pathologies. The viscoelastic solution is introduced,  
15 conveniently, through a needle at the hyperplastic tissue/retina  
16 interface. Gradual injection under pressure raises up the  
17 hyperplastic tissue. From this raised and free position, the  
18 tissue may be removed with out substantial damage to the retina  
19 tissue beneath.

20

#### METHODS

##### PURITY CRITERIA

22 All samples of hyaluronic acid obtained from Chesapeake  
23 Biologicals passed the endotoxin Limulus Lysate Assay. The  
24 criterion for passing the assay was that, when a sample was  
25 dissolved with a physiological buffer to a concentration of 5  
26 mg/ml, less than 0.25 endotoxin units per ml were found.

27

##### SURFACE TENSION

28

1        Surface tension was measured by a modification of the  
2        Wilhelmy Plate method allowing measurement of surface tension of  
3        highly viscous polymer solutions. In the Wilhelmy Plate method,  
4        the surface tension was measured by immersing a thin platinum  
5        blade into the solution to be measured. The blade is slowly  
6        withdrawn through its attachment to a surface balance. The  
7        surface balance measures the force on the platinum blade, and,  
8        as the blade is pulled from the solution, a drop in force is  
9        noted. The force is measured in dynes/centimeter. In the  
10       modified method that was used in these experiments, surface  
11       forces were measured using a sensitive transducer, (manufactured  
12       by the Honeywell Co., Minneapolis, Minnesota) attached to a  
13       platinum blade and recorder. For surface tensions measurements,  
14       about 20 ml of solutions were placed in a petri dish. The dish  
15       was placed on a jack-stand and the stand was moved upward until  
16       the platinum blade just touched the solution. With this method,  
17       surface forces were measured as the platinum blade was pulled  
18       into the solution. In the usual Wilhelmy Plate method, the  
19       surface forces are measured as the platinum blade is pulled from  
20       the solution. For reproducible results, the platinum blade was  
21       cleaned and exposed to a flame between usage. All measurements  
22       were carried out using freshly prepared solutions at  
23       temperatures of  $25^{\circ} \pm 1^{\circ}\text{C}$ .

24       In some instances, surface tension was measured at  $25^{\circ}\text{C}$   
25       using a tensiometer (Cahn, Model DCA 322, Cerritos CA). Twenty  
26       ml of a solution being tested was poured out into a Pyrex™ cover  
27       dish and placed on the stage of a tensiometer. All tests were  
28       performed at about  $17\text{-}25^{\circ}\text{C}$  ("room temperature") using a platform

1 speed of 104 microns/sec. Data was collected using an IBM-PC™  
2 and DCA-322™ software to obtain surface tension of the receding  
3 curve for the material tested.

#### 4 PREPARATION OF VISCOELASTIC SOLUTIONS

5 All polymer solutions were diluted to the desired  
6 concentration. A buffer solution containing 0.85% sodium  
7 chloride, 0.028% disodium hydrogen phosphate dihydrate and  
8 0.004% of sodium hydrogen phosphate hydrate. The dilution  
9 varied according to the desired viscosity.

##### 11 EXAMPLE 1

##### 12 Sodium hyaluronate + oleic acid

12 Hyaluronate with an average molecular weight of under  
13 50,000 (Chesapeake Biologicals) was dissolved in buffer solution  
14 at room temperature. Potassium oleate was added to achieve a  
15 final concentration of  $5 \times 10^{-6}$  mg./ml.

##### 16 EXAMPLE 2

##### 17 Acyl-substituted hyaluronate

18 Acyl-substituted hyaluronate was diluted utilizing  
19 phosphate buffer to a final concentration of 30 mg./ml.

##### 20 EXAMPLE 3

##### 21 Acyl-substituted hyaluronate + oleic acid + hyaluronate)

22 Acyl-substituted hyaluronate and hyaluronate together  
23 having an average molecular weight of  $1 \times 10^6$ , were diluted in  
24 phosphate buffer to achieve a final concentration of 30 mg./ml  
25 of sodium hyaluronate and 1 milligram per ml of acyl-substituted  
26 hyaluronate. Oleic acid was added to the final solution to  
27 achieve a concentration of  $1 \times 10^{-6}$  mg./ml. of potassium oleate.

##### 28 Example 4

### Preparation of acyl-substituted hyaluronic acid

Bioengineered hyaluronic acid from a bacterial source with an average molecular weight of 50,000 is utilized to prepare the substituted hyaluronate. Hyaluronate is dissolved in a dilute sulfuric acid solution and titrated with sulfuric acid to a final pH of 3.0. The solution is heated to 75° C and the acyl anhydride, for example N-butyric, is added to the solution. The solution is constantly stirred. The molar ratio of the two solutes is adjusted to achieve substitution of one hydroxyl group by an acyl group at every 4th to 10th repeating disaccharide unit of hyaluronic acid. The reaction is then allowed to run to completion over an extended period, approximately 24 hours. The solution is then neutralized with 0.1N sodium hydroxide and subsequently dehydrated. The resultant dried solute is used to form subsequent solutions.

Utilizing sodium hyaluronate with molecular weights in the range of 500,000 to  $2 \times 10^6$ , an acyl-substituted hyaluronate, and a biologically compatible surfactant, viscoelastic formulations can be made with any desired surface tension, which is compatible with ocular and intraocular use, and which fracture with suction forces in the range of 5 to 400 mm Hg. depending upon the solution properties desired. Unique formulations can be constructed which affect coating of ocular and intraocular structures yet which can be completely aspirated or retarded from aspiration as so desired.

### Example 5 Blending Technology

1        In order to achieve a solution with appropriate fracturing  
2 characteristics, two hyaluronic acid species of different  
3 average molecular weights were utilized. Both hyaluronic acid  
4 fractions were obtained from rooster combs from Chesapeake  
5 Biologicals. One fraction had an average molecular weight of  $1 \times 10^6$   
6 Daltons and supplied in a 5 mg/ml concentration. The  
7 other fraction consisted of an acid species with an average  
8 molecular weight of 500,000 in a concentration of 30 mg/ml. From  
9 these two species, solutions were constructed based on a volume  
10 ratio of one part low molecular weight to two part high  
11 molecular weights, hyaluronic acid. At this ratio of molecular  
12 weights, the viscous mixture easily fractured when suctioned  
13 through a 0.3 mm aspiration cannula when vacuum pressures were  
14 applied in the range of 50 to 200 mm Hg. Verification of  
15 fracturing characteristics was achieved by direct visualization  
16 through a 10X microscope.

#### 17        **Quantification**

18        Viscoelastic solutions meeting the claimed characteristics  
19 are directly determinable. Typically a solution of about 4% to  
20 about 10% viscoelastic selected from, for example, the group  
21 consisting of acyl-substituted hyaluronic acid having acyl  
22 groups thereof with three to twenty carbon atoms, hyaluronic  
23 acid, hydroxypropylmethylcellulose and mixtures thereof is  
24 useful. Clearly, higher initial percentage concentrations can  
25 be employed. Serial dilutions, conveniently in 10x steps are  
26 then made, and the viscosity and surface tension repeatedly  
27 measured until the desired point is reached. In addition,  
28 biocompatible surface active agents may be employed to reduce



1 surface tension. In mixtures of HPMC and hyaluronic acid, and  
2 derivatives thereof, it is useful to note that HPMC contributes  
3 little to viscosity while possessing surface activity, while  
4 hyaluronic acid and derivatives thereof contribute substantially  
5 to viscosity and little to surface activity. In practice a  
6 checkerboard dilution and proportion type assay provides a  
7 convenient system for determining component proportions within  
8 the claimed range. The accompanying graphs, particularly Figs.  
9 6 and 7 will assist in the interpretation of checkerboard  
10 results by directing one to the proper parameter by modification  
11 of the proper constituent.

#### 12 **Viscosity Measurements**

13 Tested solutions were removed from storage at 4°C and  
14 allowed to reach room temperature. After reaching room  
15 temperature, 5ml of such solution was injected onto the sample  
16 testing plate of a viscometer, Rheometrics Fluids Spectrometer  
17 #RFS8400™ (Piscataway, N.J.). The shear rate was linearly  
18 increased from 0.3 sec<sup>-1</sup> to 9.0 sec<sup>-1</sup> over a period of 9  
19 minutes,  
20 and the viscosity of the solution recorded with a Haake RV 100  
21 plotter. From a plot of viscosity v. shear rate, the viscosity  
22 at 0.35 sec<sup>-1</sup> was extrapolated.

#### 23 **Molecular Weight**

24 Molecular weight may be determined by any of a number of  
25 well known techniques such as chromatography and density  
26 centrifugation. A particularly useful method of measuring  
27 molecular weight was by the scattered light intensity at an  
28 angle of 6-7° using a Chromatic KMX-6™ laser light scattering

1 device. A detailed description of this method is set forth in  
2 "Laser Light Scattering measurements on Vitreous and Rooster  
3 Comb Hyaluronic Acids," Int.J.Biol.Macromol., 4:425-9 (1982)  
4 incorporated herein by reference. The Optical constant required  
5 for molecular weight determinations was obtained using a  
6 chromatix KMC-16™ differential refractometer operating at 5°C  
7 and at a wavelength of 633nm. The instrument was calibrated by  
8 measuring the difference in the refractive index of standard  
9 salt solutions with water as the reference material. Once the  
10 calibration constant was determined from measurements on salt  
11 solutions, the difference in refractive index between each  
12 solution and its dialysate was measured at concentrations  
13 between 1 and 5mg/ml. The ratio of change in refractive index,  
14  $\Delta n$ , divided by the concentration,  $c$ , was plotted against  
15 concentration and the value of the refractive index was taken as  
16  $\Delta n/c$  extrapolated to zero concentration.

17 Molecular weight was then obtained by determining the  
18 Rayleigh factor, ( $R_\theta$ ) for solutions of unknown concentration,  $c$ ,  
19 between 0.1 and 0.5 mg/ml and plotting  $Kc/R_\theta$  against  
20 concentration ( $K$ , the optical constant is calculated using  
21 refractive index increment) as shown in Fig. 1, with a  
22 calculated molecular weight of 5,560,000. Weight average  
23 molecular weight was determined from the reciprocal of  $Kc/R_\theta$   
24 extrapolated to zero concentration.

#### 25 Injection Tests

26 A particular injection load versus time curve is set forth  
27 in Fig. 2. The material tested was a high molecular weight HA.  
28 Maximum load was determined as the largest load needed to force

1 the sample from a syringe through a 23 gauge needle. While  
2 testing may be accomplished various ways known in the art, HA  
3 and HPMC solutions were conveniently tested using a syringe  
4 holder fashioned to attach to the compression cell of an Instron  
5 Tester Model 1122 (Instron Corp, Springfield, N.J.). Force was  
6 measured from the load cell and the crosshead was lowered at a  
7 rate of 200mm/min. Maximum stress was determined by dividing  
8 the peak load by the cross sectional area (interior) of the  
9 syringe barrel.

#### 10 **Aspiration Profile**

11 Aspiration behavior was uniformly determined by use of a 23  
12 gauge needle. Test procedure entailed placing a vacuum through  
13 the 23 gauge needle onto each sample and determining the  
14 fraction of each sample aspirated within 1 minute. The vacuum  
15 was increased in 22 mm Hg increments from 0 to 100 mm Hg and the  
16 fraction aspirated was determined gravimetrically. From the  
17 data represented in Fig. 5, the distinct aspiration  
18 characteristic of the viscoelastic solutions of this invention  
19 are made clear. The inventive solutions do not aspirate as a  
20 bolus at any applicable vacuum level. Of particular importance  
21 is the substantially non-sigmoidal curve found upon aspiration  
22 of solutions of this invention under the conditions used in  
23 compiling the data of Fig. 5. In contrast, HA solutions of  
24 comparable viscosity, aspirate as bolus at all but the lowest  
25 vacuum levels. In practice, at aspiration vacuum levels  
26 designed to provide reasonably prompt removal of less than the  
27 total amount of viscoelastic solution, only the inventive  
28 solutions will suffice. The shaded area of Fig. 5(a) generally

1 delimits the particular aspiration characteristic of less than  
2 total aspiration of viscoelastic solution of the present  
3 invention at vacuum levels above about 50 mm Hg. The aspiration  
4 curves at the vacuum levels tested offers reasonable  
5 predictability as to those aspiration characteristics that will  
6 permit a medical professional to incrementally aspirate a  
7 viscoelastic at convenient pressures and over a fairly brief  
8 period of time. Solutions with sigmoidal curves aspirate  
9 essentially as a bolus and are not suitable. In the 50 to 90  
10 mmHg range under this procedure, and limited to solutions that  
11 are substantially non-sigmoidal in aspiration behavior, a slope  
12 of from about horizontal up to about 1.5 and more particularly  
13 from about horizontal to about 1.0 are preferred, with a slope  
14 or aspiration profile of about horizontal to about 0.5 more  
15 preferred. It is understood that the slope of an horizontal line  
16 is technically an undetermined special case. However, a  
17 slightly upward line has a slope of a small positive number.  
18 For convenience here, the slope of an horizontal line will be  
19 assumed to be zero, and the stated range from horizontal up to  
20 slopes of 1 and 1.5, includes horizontal (or even slightly  
21 negative slopes). While very high or low vacuum levels or  
22 aspiration times are conceivable, they are less useful, except  
23 in unique circumstances. Unduly high aspiration vacuum levels  
24 pose a danger to ocular structures. Unduly long aspiration  
25 times, generally in excess of 2 or 3 minutes, unduly prolong  
26 surgical procedures.

27

28

1 Again referencing Fig. 7, Aspiration profile is presented  
2 in Z axis, forming, as plotted against viscosity and surface  
3 tension a theoretical cube of the claimed viscoelastic solution.  
4 Points A, B, C and D are at a viscosity of 100,000 mPa.s.  
5 Points E, F, G, and H are at a viscosity of 10,000 mPa.s.  
6 Points A, D, E, and H are at Aspiration Profile of 0. Points B,  
7 C, F, and G are at Aspiration Profile points of 1.5. Points A,  
8 B, E, and F are at Surface Tension of 40 dynes/cm. Points D, C,  
9 H and G are at Surface Tension of 65 dynes/cm. Point I  
10 represents Occucoat and point II represents Healon, each beyond  
11 the enclosed area.

12 With the techniques and examples described above, the novel  
13 and unobvious modified mucopolysaccharide solutions of this  
14 invention are presented in the claims which follow. Minor  
15 changes and adjustments may be made by those skilled in the art  
16 without departing from the spirit of this invention.  
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28

TABLE 1. *Products and solutions used or tested for use in ophthalmic surgery*

Product	Manufacturer	Polymer	Concentration	Molecular weight
Healon	Pharmacia	HA	10	~4,000,000
Amvisc	Med-Chem Products	HA	~10	~2,500,000
IaL	Fidia	HA	20	~500,000
Viscoat	Cilco	HA +	30	~500,000
		CS	40	~30,000
CS 50%	—	CS	500	~20,000
HPMC 2%	—	HPMC	20	~100,000
Collagen	3M	Collagen	20	320,000 → gel

HA—hyaluronan, CS—Chondroitin sulphate,  
 HPMC—hydroxypropylmethylcellulose.

1  
2  
3 **WHAT IS CLAIMED;**

4 Claim 1. The modified mucopolysaccharide solution for use  
5 as a biologically active therapeutic infusion comprising:

6 a pharmaceutical grade viscoelastic fraction selected from  
7 the group consisting of acyl-substituted hyaluronic acid having  
8 acyl groups thereof with three to twenty carbon atoms,  
9 hyaluronic acid, hydroxypropylmethylcellulose and mixtures  
10 thereof, and absent chondroitin sulfate said fraction having a  
11 surface tension of between 40 and 65 dynes/cm<sup>2</sup>; and,

12 said modified mucopolysaccharide solution having a  
13 viscosity of between 10,000 and 100,000 centipoise when measured  
14 at a shear rate of 3 sec<sup>-1</sup> at 25°C.

15 Claim 2. A modified mucopolysaccharide solution as  
16 described in Claim 1 having a surface tension of less than about  
17 56 dynes/cm<sup>2</sup>.

18 Claim 3. A modified mucopolysaccharide solution as  
19 described in Claim 2 having a surface tension of less than about  
20 50 dynes/cm<sup>2</sup>.

21 Claim 4. A modified mucopolysaccharide solution as  
22 described in Claim 1 wherein said viscoelastic fraction has an  
23 average molecular weight of at least 50,000.

24 Claim 5. A modified mucopolysaccharide solution as  
25 described in Claim 1 wherein said viscoelastic fraction is an  
26 acyl-substitute hyaluronic acid having acyl groups thereof with  
27 three to twenty carbon atoms.  
28

Claim 6. A modified mucopolysaccharide solution as described in Claim 1 wherein said solution further includes a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in an amount sufficient to produce said surface tension.

Claim 7. A modified mucopolysaccharide solution as described in Claim 6 wherein said solution further includes a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in an amount less than 10 micrograms/ml.

Claim 8. The modified mucopolysaccharide of Claim 7 wherein said surfactant fraction of a biocompatible component is a free fatty acid.

Claim 9. A modified mucopolysaccharide solution as described in Claim 4 wherein said viscoelastic fraction is a mixture of said acyl-substituted hyaluronic acid and hyaluronic acid.

Claim 10. A modified mucopolysaccharide solution as described in Claim 9 wherein said solution further includes a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants, said surfactant present in an amount sufficient to produce said surface tension.



Claim 11. A modified mucopolysaccharide solution as described in Claim 10 wherein said solution further includes a surfactant fraction of a biocompatible component selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, nonionic surfactants, said surfactant present in an amount less than 10 micrograms/ml.

Claim 12. The modified mucopolysaccharide solution of Claim 1 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 13. The solution of Claim 12 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 14. A modified mucopolysaccharide solution as described in Claim 12 further including the surfactant is oleic acid.

Claim 15. The modified mucopolysaccharide of Claim 12 wherein said surfactant fraction of a biocompatible component is a free fatty acid.

Claim 16. A modified mucopolysaccharide solution for use during ophthalmic surgery for protection of the internal ocular structures including corneal endothelium from accidental touch by surgical instruments, yet permitting of observation of said structures comprising:

an optically clear polymeric fraction of high purity mucopolysaccharides selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with

three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction having a surface tension of between 40 and 65 dynes/cm<sup>2</sup>; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec<sup>-1</sup> at 25 C; and,

wherein said mucopolysaccharide fraction has an average molecular weight of at least 50,000; and,

a biological surfactant fraction of a free fatty acid present in an amount less than 10 micrograms/ml.

Claim 17. A modified mucopolysaccharide solution as described in Claim 16 having a surface tension of less than about 56 dynes/cm<sup>2</sup>.

Claim 18. A modified mucopolysaccharide solution as described in Claim 17 having a surface tension of less than about 50 dynes/cm<sup>2</sup>.

Claim 19. A modified mucopolysaccharide solution as described in Claim 16 wherein said polymeric fraction is hyaluronic acid.

Claim 20. The modified mucopolysaccharide solution of Claim 16 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 21. The solution of Claim 20 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 22. A pharmaceutically acceptable modified mucopolysaccharide solution absent chondroitin sulfate having a surface tension of between 40 and 65 dynes/cm<sup>2</sup>; and,

a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec<sup>-1</sup> at 25 C.

Claim 23. A modified mucopolysaccharide solution as described in Claim 22 having a surface tension of less than about 56 dynes/cm<sup>2</sup>.

Claim 24. A modified mucopolysaccharide solution as described in Claim 23 having a surface tension of less than about 50 dynes/cm<sup>2</sup>.

Claim 25. The solution of claim 22 wherein said mucopolysaccharide is a surface active mucopolysaccharide.

Claim 26. The solution of claim 25 further comprising a biological surfactant selected from a group consisting of phospholipids, monoglycerides, free fatty acids, free fatty acid soaps, cholesterol, fluorocarbons, silicones, and nonionic surfactants.

Claim 27. The solution of Claim 22 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 28. The solution of Claim 27 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 29. The solution of Claim 22 wherein said mucopolysaccharide has an average molecular weight of at least 50,000.

Claim 30. The solution of Claim 29 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 31. The solution of Claim 30 wherein, upon aspiration through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 32. A method of protecting internal ocular structures during ocular surgery and retarding aspiration of material from the ocular surgery site by the step of:

intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction with a surface tension of between 40 and 65 dynes/cm<sup>2</sup>; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec<sup>-1</sup> at 25 C.

Claim 33. The method of Claim 32 wherein the intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution is by a syringe of about 0.16 cm<sup>2</sup> in cross section or less.

Claim 34. The method of Claim 32 wherein the modified mucopolysaccharide solution has a surface tension of less than about 56 dynes/cm<sup>2</sup>.

Claim 35. The method of claim 34 wherein the modified mucopolysaccharide solution has a surface tension of less than about 50 dynes/cm<sup>2</sup>.

Claim 36. The method of claim 32 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 37. The method of claim 36 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 38. A method of protecting internal ocular structures during ocular surgery by providing a viscoelastic solution that coats ocular structures at a surgical site such that aspiration of the viscoelastic solution is retarded, said method being:

intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution absent chondroitin sulfate and having a surface tension of between 40 and 65 dynes/cm<sup>2</sup>; and,

a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec<sup>-1</sup> at 25 C.

Claim 39. The method of Claim 38 wherein the intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution is by a syringe of about 0.16 mm in cross section or less.

Claim 40. A modified mucopolysaccharide solution as described in Claim 38 having a surface tension of less than about 56 dynes/cm<sup>2</sup>.

Claim 41. A modified mucopolysaccharide solution as described in Claim 40 having a surface tension of less than about 50 dynes/cm<sup>2</sup>.

Claim 42. The method of claim 41 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 43. The method of claim 42 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 44. A method of protection of internal ocular structures including corneal endothelium from accidental touch by surgical instruments, yet permitting of observation of said structures comprising:

intraocularly introducing a modified mucopolysaccharide solution during ophthalmic surgery wherein said solution comprises

an optically clear polymeric fraction of high purity mucopolysaccharides selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof and absent chondroitin sulfate, said fraction having a surface tension of between 40 and 65 dynes/cm<sup>2</sup>; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of  $3 \text{ sec}^{-1}$  at 25 C; and,

wherein said mucopolysaccharide fraction has an average molecular weight of at least 50,000; and,

a biological surfactant fraction of a free fatty acid present in an amount less than 10 micrograms/ml.

Claim 45. The method of Claim 44 wherein the intraocularly introducing biologically active therapeutic infusion amount of a modified mucopolysaccharide solution is by a syringe of about 0.16 mm in cross section or less.

Claim 46. The method of claim 44 wherein the retarding of aspiration being such that, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 5 to 400 mm Hg, said solution is easily fractured.

Claim 47. The method of claim 46 wherein said solution, upon aspirating through a 0.3 mm cannula at a vacuum pressure in a range of 50 to 200 mm Hg, said solution is easily fractured.

Claim 48. A modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm<sup>2</sup>; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of  $3 \text{ sec}^{-1}$  at  $25^{\circ}\text{C}$ .

Claim 49. A modified mucopolysaccharide solution as described in Claim 48 having a surface tension of less than about  $56 \text{ dynes/cm}^2$ .

Claim 50. A modified mucopolysaccharide solution as described in Claim 47 having a surface tension of less than about  $50 \text{ dynes/cm}^2$ .

Claim 51. A modified mucopolysaccharide solution for use as a biologically active therapeutic infusion as delimited by the shaded area of Fig. 7.

Claim 52. A method of adhering a contact lens to the surface of the eye in operational-optical connection with said eye, by the step of interposing between said lens and said eye surface an adhering amount of substantially transparent modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65  $\text{dynes/cm}^2$ ; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of  $3 \text{ sec}^{-1}$  at  $25^{\circ}\text{C}$ .



Claim 53. A method of hydraulically positioning intra-optic structures or tissues by the step of applying against such tissues under elevated hydrostatic pressure modified mucopolysaccharide solution for use as a biologically active therapeutic infusion comprising:

a pharmaceutical grade viscoelastic fraction selected from the group consisting of acyl-substituted hyaluronic acid having acyl groups thereof with three to twenty carbon atoms, hyaluronic acid, hydroxypropylmethylcellulose and mixtures thereof, and absent chondroitin sulfate said fraction having a surface tension of between 40 and 65 dynes/cm<sup>2</sup>; and,

said modified mucopolysaccharide solution having a viscosity of between 10,000 and 100,000 centipoise when measured at a shear rate of 3 sec<sup>-1</sup> at 25°C.

Claim 54. The method of Claim 53 wherein the tissue is hyperplastic tissue, positioned over the retina and said applying is performed by injecting said solution between said tissue and the retina, said positioning resulting in raising the tissue off of the retina.

FIG. 1

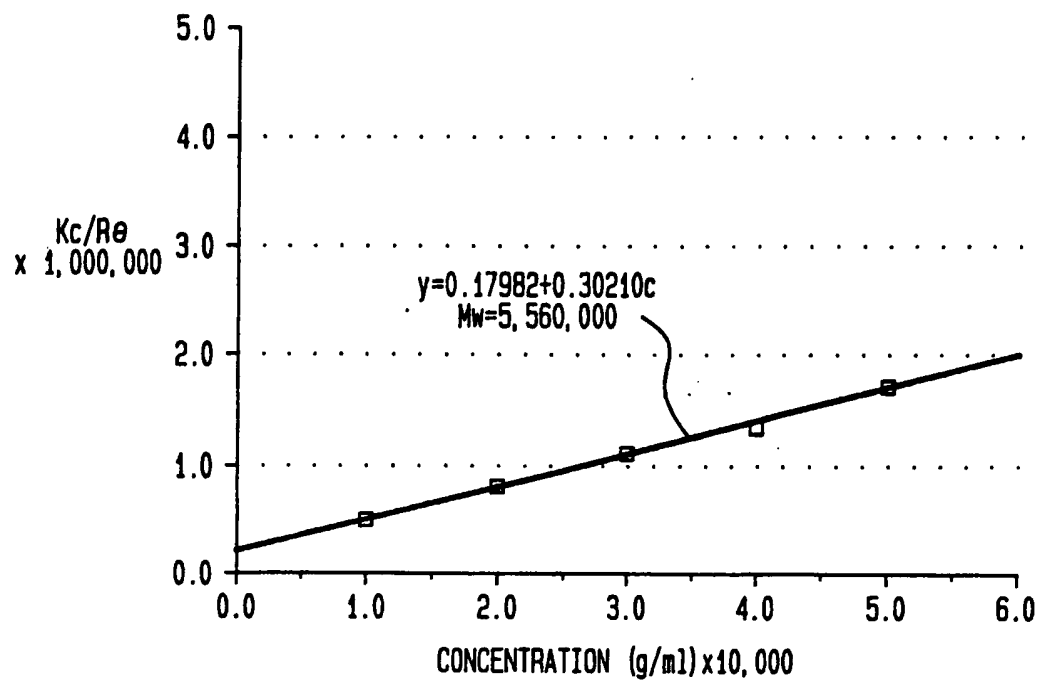


FIG. 2

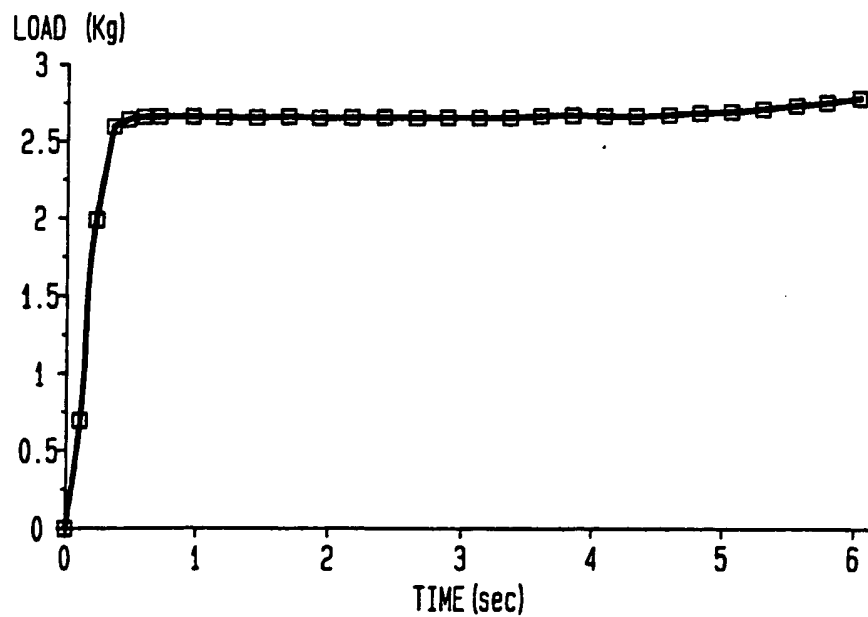


FIG. 3

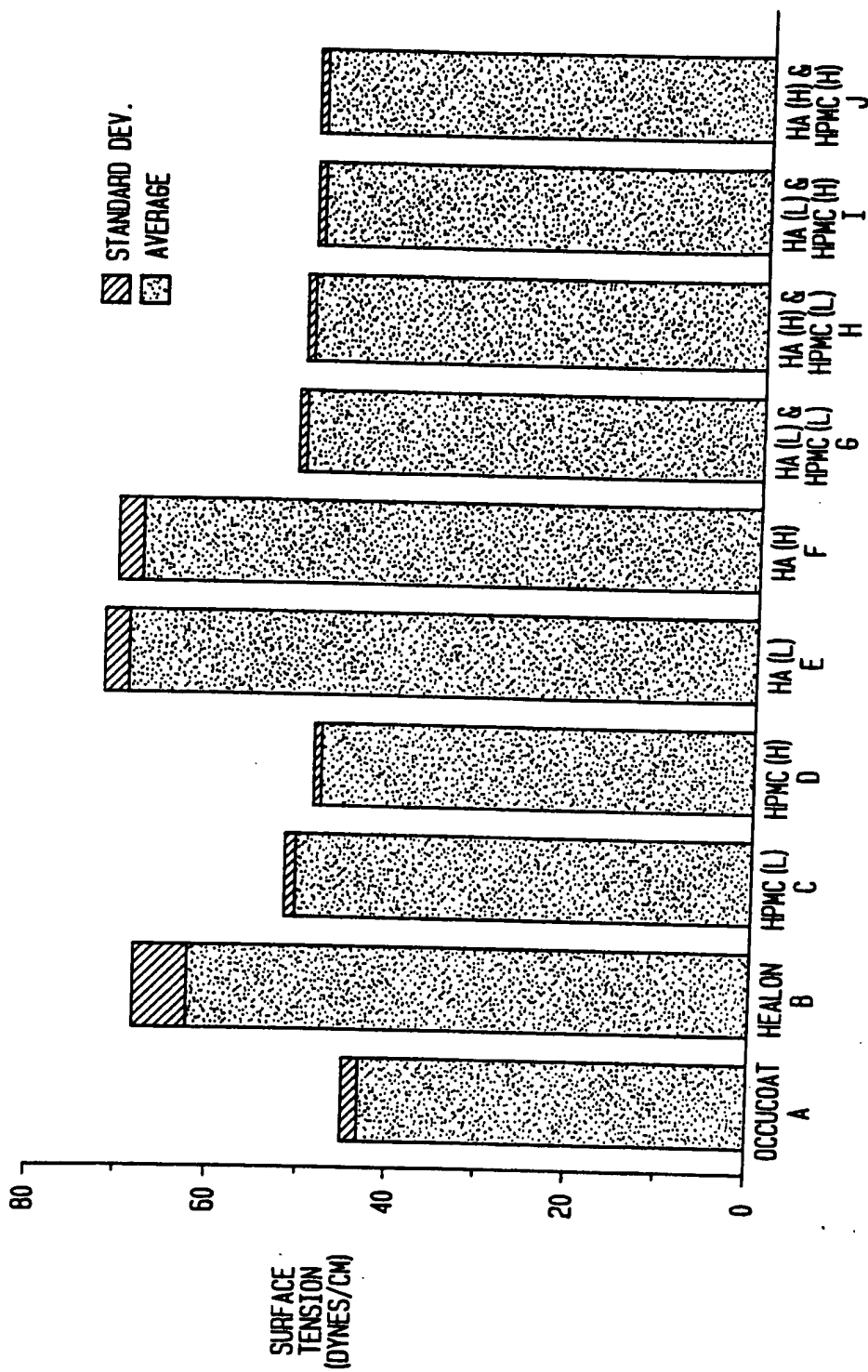


FIG. 4

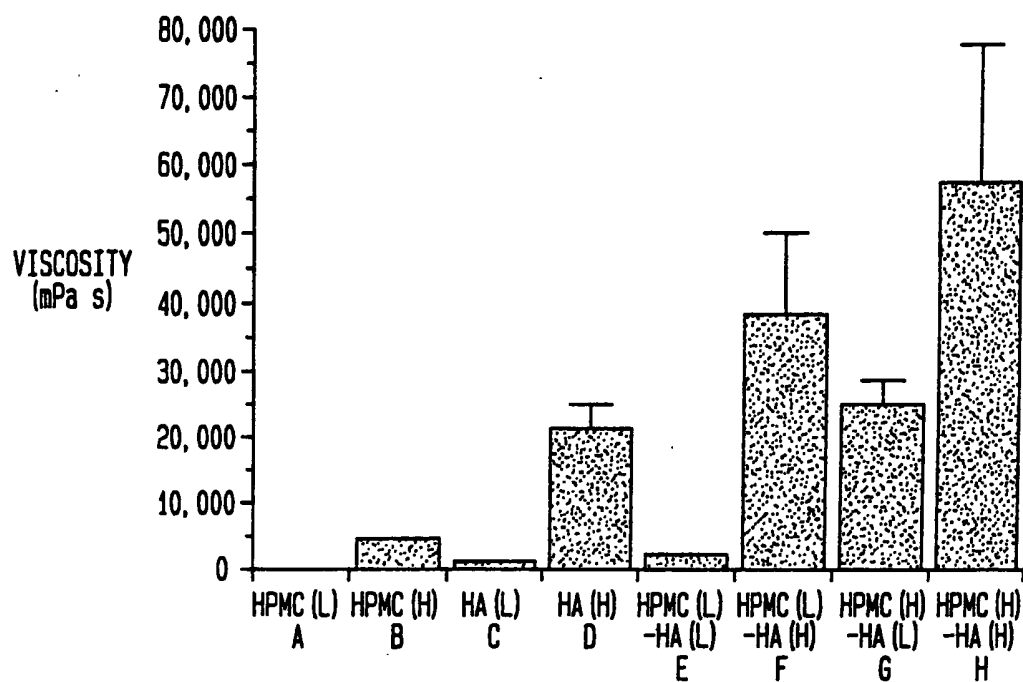


FIG. 5

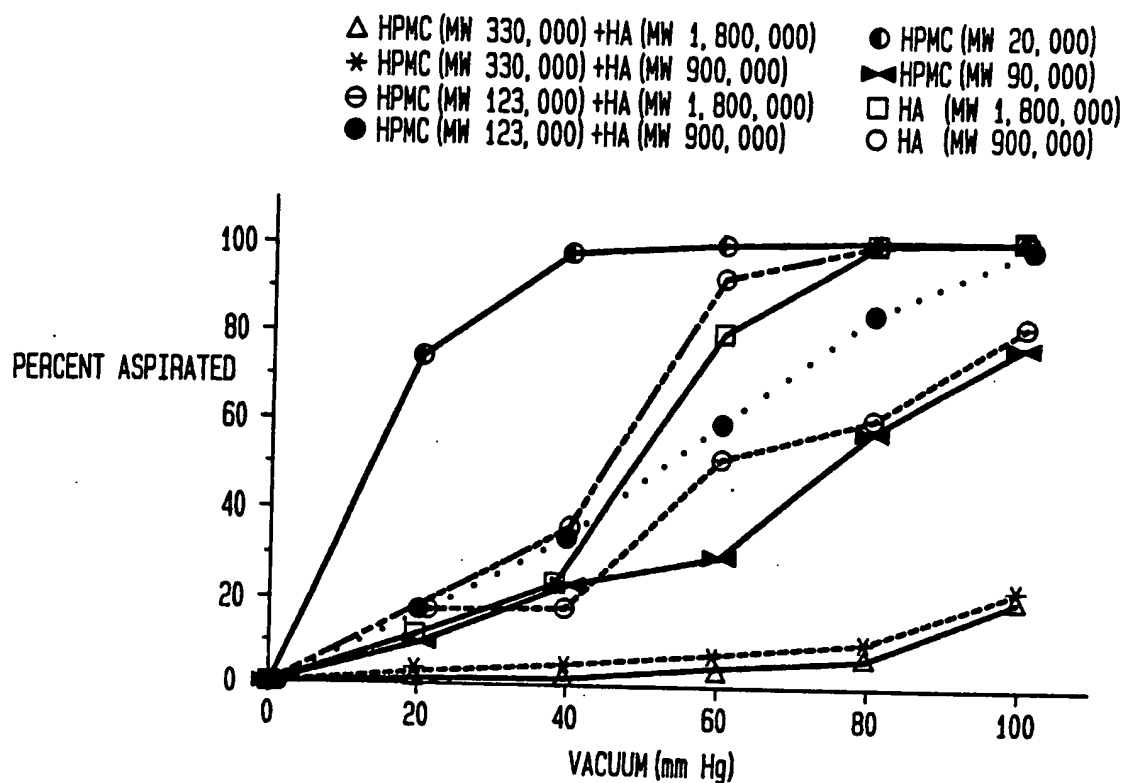


FIG. 5A

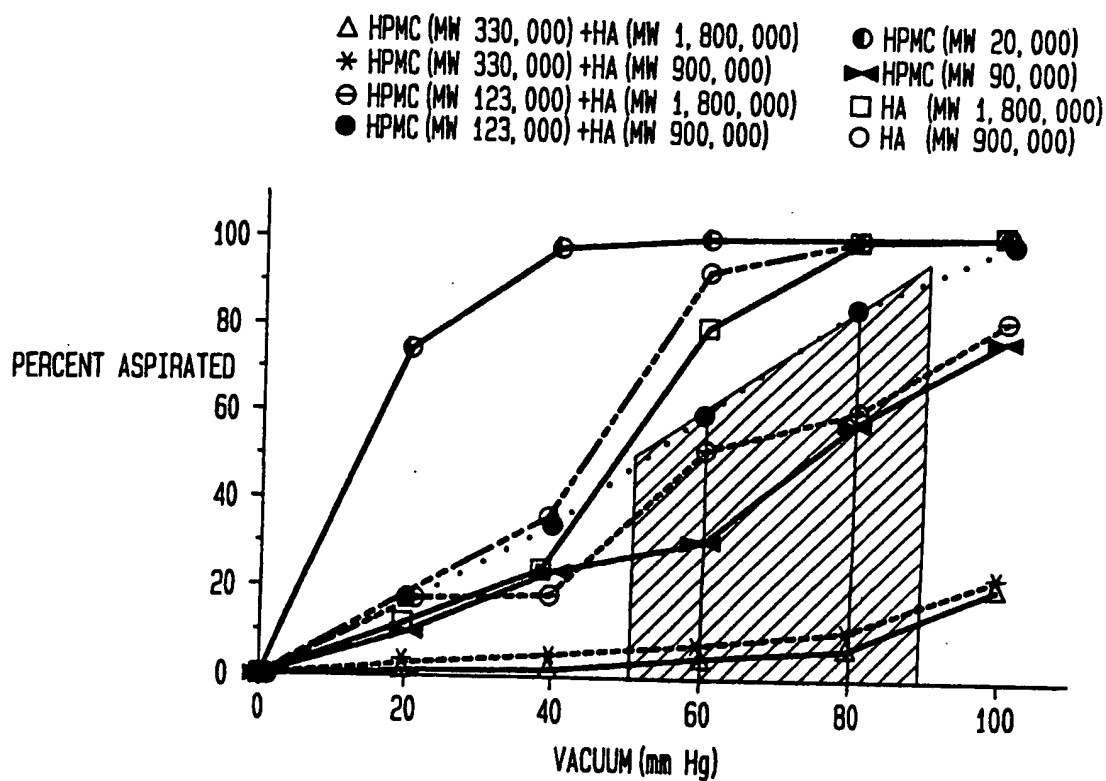


FIG. 6

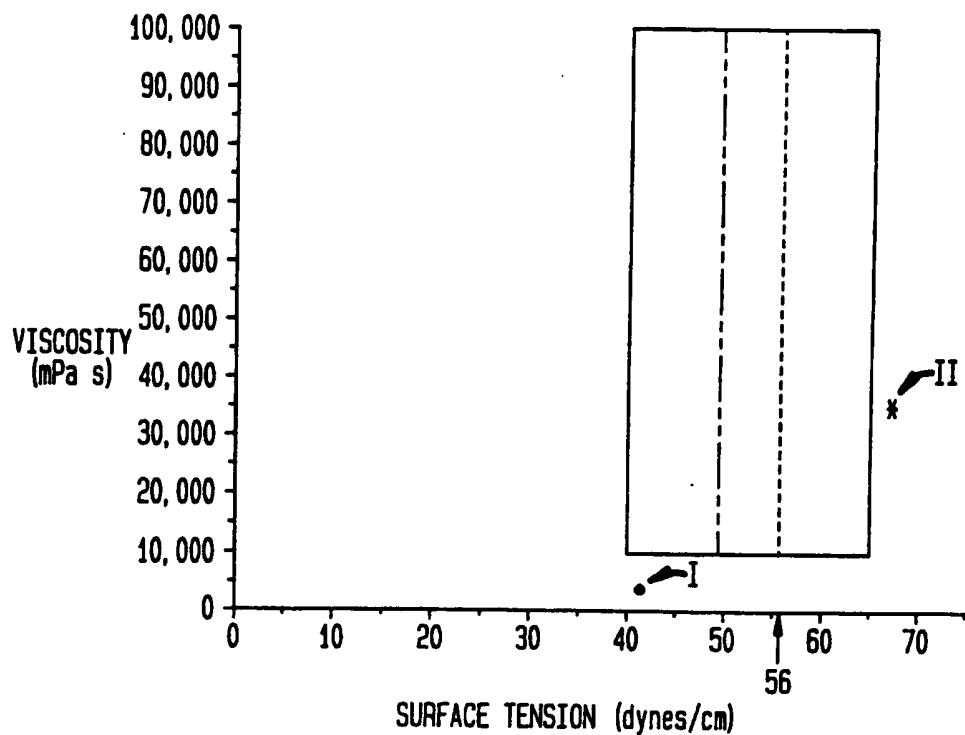


FIG. 7

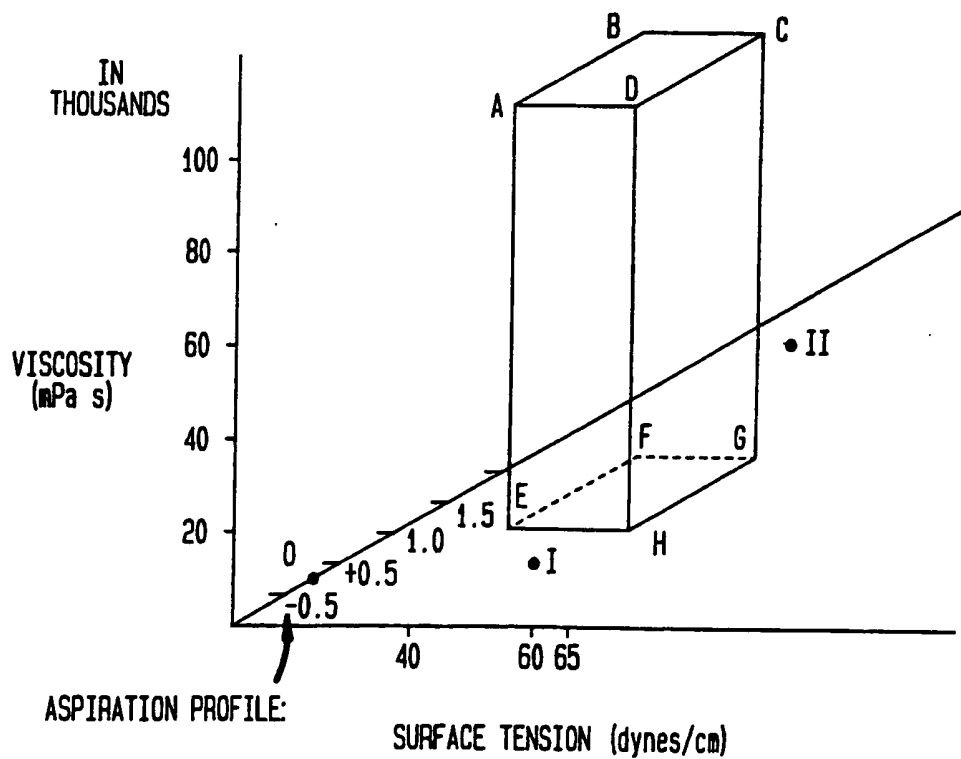


FIG. 8

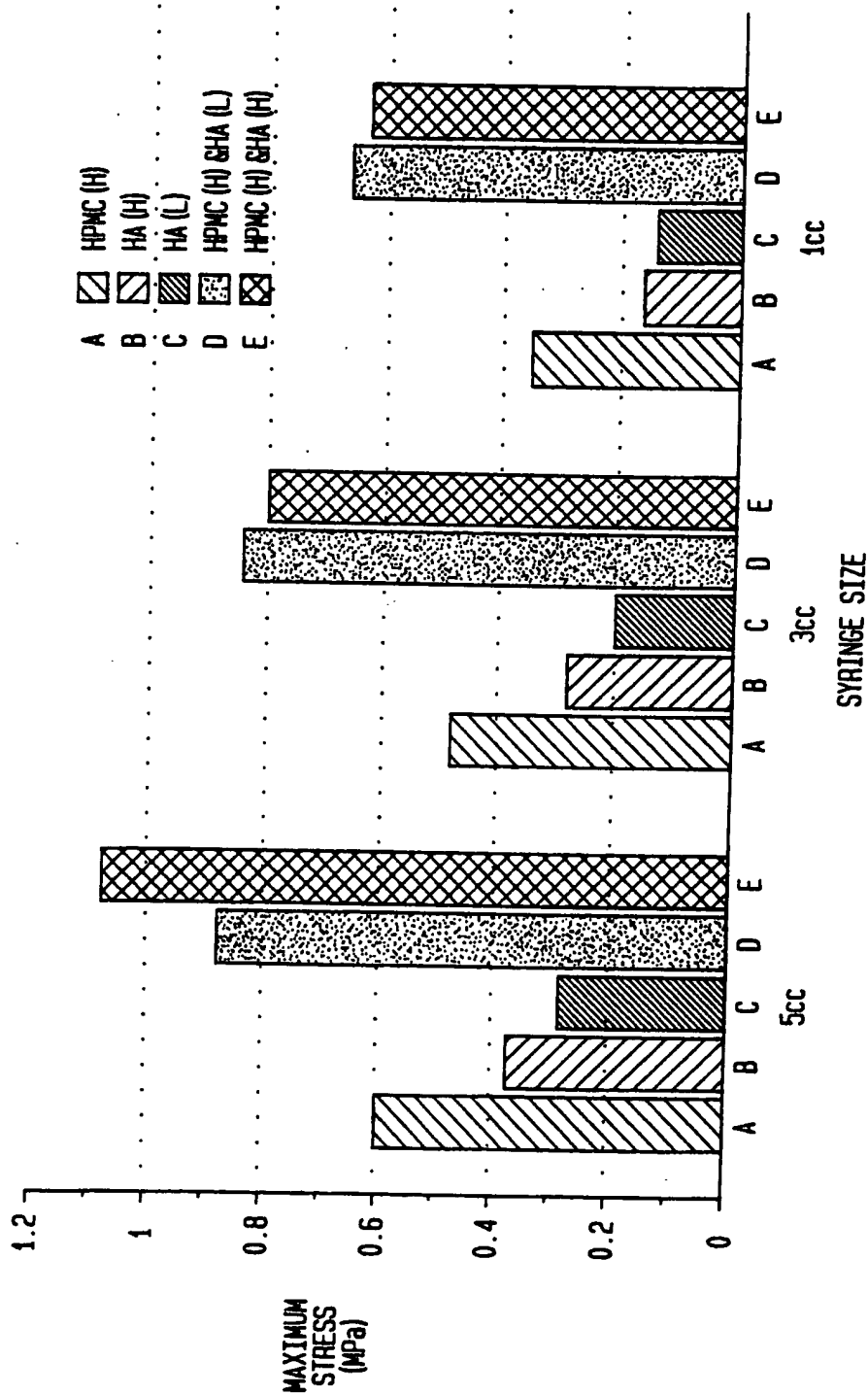


FIG. 9A

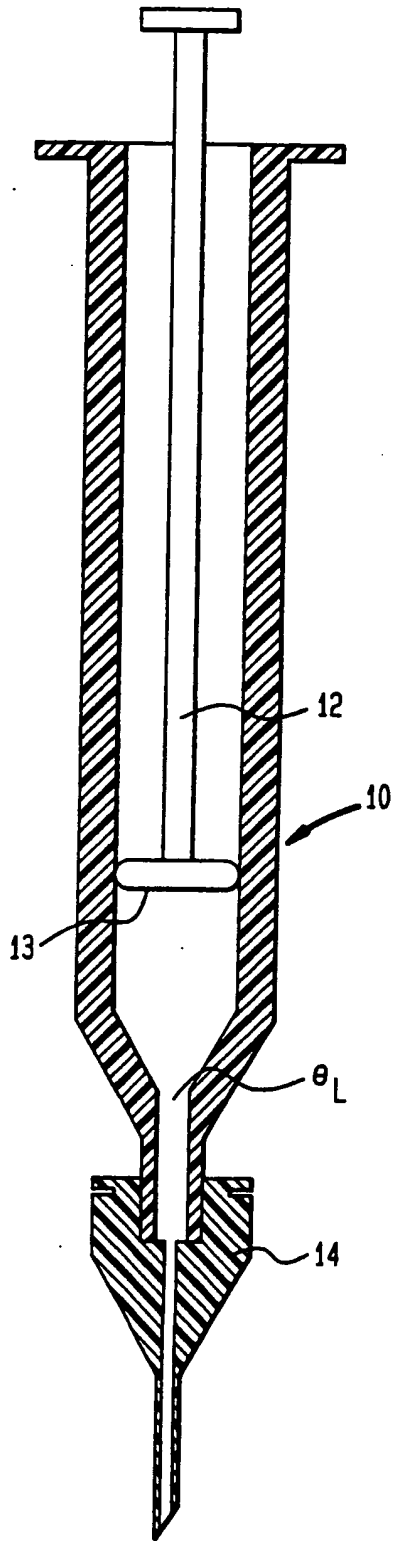


FIG. 9B

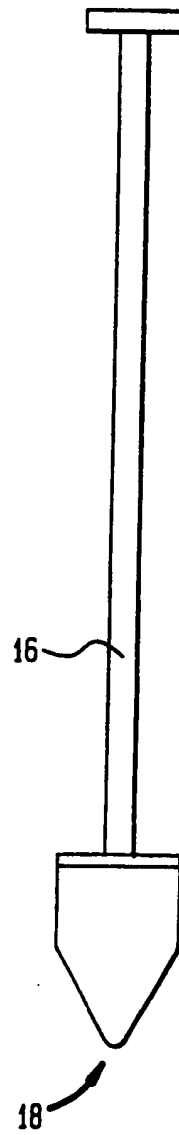


FIG. 9C

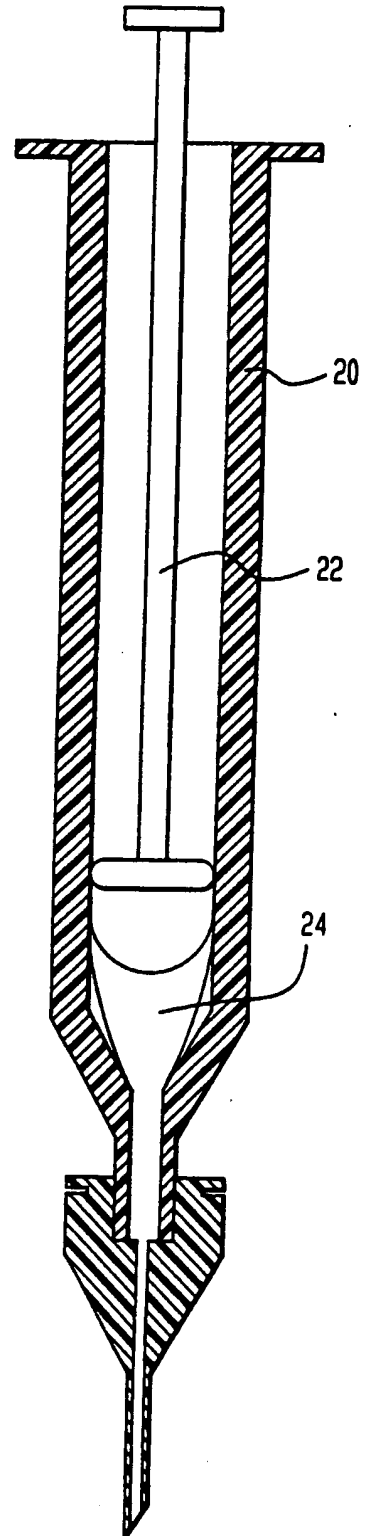




FIG. 10A

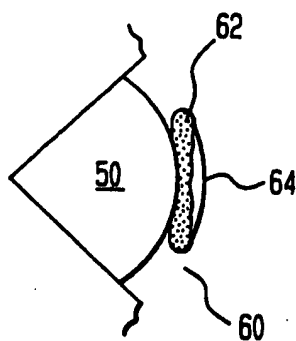
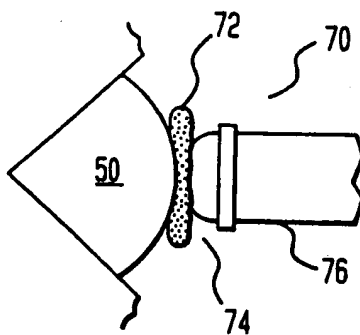


FIG. 10B



# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US94/10175

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/70; A61F 13/20; G02C 7/02

US CL : 514/54; 351/177; 604/19

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/54; 351/177; 604/19

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
APS, CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,713,375 (LINDSTROM ET AL.) 15 December 1987, col. 1, lines 22-37 and col. 2, lines 1-3.	1-51
Y	US, A, 4,767,463 (BRODE ET AL.) 30 August 1988, col. 12, lines 17-42.	6-8, 10-11, 26
Y	US, A 4,851,521 (DELLA VALLE ET AL.) 25 July 1989, col. 1, lines 48-68, col. 3, lines 3-59.	1-51
Y	Survey of Ophthalmology, Volume 34, No. 4, issued January-February 1990, Liesegang et al, "Viscoelastic Substances in Ophthalmology", pages 268-293, especially pages 269-272.	1-51

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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Date of the actual completion of the international search

02 DECEMBER 1994

Date of mailing of the international search report

DEC 28 1994

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